Differential Diagnosis

THE INTERPRETATION OF CLINICAL EVIDENCE

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PREFACE

THE objectives and scope of this book are set forth in some detail in the *Introduction* The subject—differential diagnosis—pervades such a broad field and provides a common meeting ground for so many medical disciplines that our greatest problem has been to keep our material within reasonable bounds Having decided upon the topics which would satisfactorily illustrate the diagnostic principles which we had in mind it was necessary to select from the case records of several hundred clinical pathological conferences those which would best serve our purpose Some ninety cases were chosen We tried to exclude those in which the diagnostic analysis required tedious repetition of arguments previously presented In this we were only partially successful for the process of differential diagnosis neces sarily involves almost endless recapitulation of past experience as each new problem is faced The reader not only will observe some unavoidable duplication in the case analyses but he will doubtless be impressed by the frequency with which even in this relatively small group of cases a single disease entity is encountered in different guises The appearance of such multiform diseases as tuberculosis and lymphosarcoma in each of several chapters is not an accident of selec tion but an aspect of differential diagnosis worthy of particular attention

In the choice of cases we have given preference to those in which the clinical studies were carried out during the past ten years This was done so as to include the diagnostic procedures currently in use However exclusion of all e rlier cases would have deprived us of much interesting and sometimes unique material It will be found therefore that the chronological span of the cases is quite wide and that this leads at times to a disconcerting lack of uniformity particu larly in the documentation of some of the ancillary examinations For

example hemoglobin values may be expressed in one case in percentage of a hypothetical normal and in another in grams per 100 ml, blood electrolytes may be expressed in milligrams per 100 ml or in milliequivalents per liter It must also be borne in mind that in the earlier cases the interpretation of electrocardiograms was based upon a study of only the three standard limb leads with the occasional addition of a single precordial lead We have recorded all these and other findings and interpretations just as they appeared in the original case histories since these records provided the basis for the discussion at the clinical pathological conferences

The clinical histories physical examinations and progress notes are condensed versions of the abstracts prepared for the conferences Through this double condensation they have been shorn of the niceties of clinical description which were evident in many of the original records This concession to space requirements presents the facts in such concentrated form that their assimilation is not always an easy task Similarly the reports of the autopsy findings have been severely condensed both by abbreviating the original descriptions and by deleting many unessential details We are indebted particularly to Dr Arnold R Rich who participated in most of these clinical pathological conferences for making the autopsy reports available to us However we must accept full responsibility for the condensed form in which the reports appear We regret that they lack the completeness and lucidity of Dr Rich s presentations at the conferences

After giving much thought to the desirability of including illustrative material such as x ray pictures electrocardiograms and photographs of autopsy findings it was finally concluded that these otherwise valuable features were not essential to the attainment of our primary objective Since they would have added materially to the bulk of the volume and would have increased considerably the cost to the reader it was decided not to include them

We wish to acknowledge our great indebtedness to the many medical students house officers attending physicians and consultants whose clinical histories physical examinations progress notes and comments created the vast store of case material from which we have been able to draw To list them individually would be an insurmountable task we therefore thank them collectively and gratefully acknowledge that without their basic contributions this book could not have been written

We have noted in the *Introduction* our special indebtedness to the late Dr Louis Hamman whose posthumous contributions to our

methods of procedure place him almost in the position of a co author We recognize another incalculable debt to the late Dr Warfield T Longcope on whose service at the Johns Hopkins Hospital we both served as Medical Residents and later as associates and from whom we derived our interest in many of the topics discussed in this book

Grateful acknowledgment of assistance in preparing the manu script and reading the proof is due our respective secretaries Miss Catherine Hanley of Baltimore and Mrs Beatrice O Connell of Cooperstown Dr Leighton Cluff Resident Physician of the Johns Hopkins Hospital gave invaluable assistance in reviewing the proof and in going back to original sources to verify factual details

Finally we wish to thank our publishers who have done much to simplify and lighten the later phases of our task

A McGehee Harvey
James Bordley III

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INTRODUCTION

I

> The patient is requested to hold a saucer which a wick is lighted The medicine man the flame and with every grain calls out the The first grain that catches fire indicates w the illness *

The simple routine described above practic of India is typical of the diagnostic methods c peoples The procedure was an objective and conclusions drawn therefrom were self evident as to the medicine man No accumulation of quired and the diagnosis was attained with Magic and divination alone were necessary Pe that has led many laymen to look upon the possessed of a medical divining rod—a perso serving certain portents and stigmata can con label called a diagnosis This view is foste understanding about how sound medical concl by the uncertain connotation of the term *diag*

The noun *diagnosis* is derived from Greek tinguish or discern In the English usage of t turies the *diagnostics* of a disease were the feat be recognized The distinguishing signs and it generally begins continues and goes off of the Disease The diagnostics of the Bite described as follows

* Sigerist A History of Medicine

The consequences of this bite are flying pains over all the body especially about the wounded part pensiveness and sadness irrascibility intermitting pulse tremors and contractions of the nerves inward heat and thirst and after some time an *hydrophobia* and convulsions at the sight of any liquids what soever which is supposed to be an infallible and univocal sign of this poison *

As may be noted from the quotation *diagnostics* in this 18th century text was synonymous with *nosography*

In common modern usage *diagnosis* is the identification of a dis ease by investigation of its signs and symptoms In medical termi nology however the precise meaning of the word is obscured by the many ways in which it is used clinical diagnosis laboratory diag nosis physical diagnosis anatomical diagnosis bacteriological diag nosis x ray diagnosis electrocardiographic diagnosis and the like In each of these cases the word *diagnosis* connotes an appreciation of the meaning of observations made by particular methods But it does not necessarily signify the identification of a disease by these means For example physical diagnosis comprises a group of pro cedures directed toward the determination of the state normal or abnormal of various organs Anatomical diagnosis as employed in most pathology laboratories consists in the recapitulation in brief descriptive terms of the principal anatomical lesions observed at autopsy The lesions which are noted may or may not identify a disease Without further elaboration of the subject it is understand able that when the physician employs the term *diagnosis* he may have in mind any one of several concepts This being the case it may be well for us to state what we mean by the expressions *diagnosis* and *differential diagnosis*

Diagnosis when not preceded by a qualifying adjective means to us the identification of a disease by the investigation of its manifesta tions Since a diagnosis may be made on the basis of the best available evidence it does not signify the positive and unequivocal identifica tion of a disease Although *diagnosis* has been defined in one of its meanings as the art of distinguishing one disease from another, we prefer to add the qualifying word *differential* when we have this meaning in mind Richard C Cabot who did so much to illuminate this subject called differential diagnosis a very dangerous topic — dangerous to the reputation of physicians for wisdom It is I sup pose owing to this danger that so little has been written on differential diagnosis and so much on *diagnosis* (non differential) To state the symptoms of typhoid perforation is not difficult To give a set of rules whereby the conditions which simulate typhoid perforation may be

* Shaw A New Practice of Physic

excluded is exceedingly difficult Physicians are very naturally reticent on such matters slow to commit their thoughts to paper and very suspicious of any attempt to tabulate their methods of reasoning Yet all diagnosis must become differential before it can be of any use

Two methods of teaching differential diagnosis have helped to remove this subject from the realm of dogma These are the bedside clinic and the clinical pathological conference It is not often realized that the distinguished physiologist Walter B Cannon when he was a student in the Harvard Medical School was the first to suggest what he called the case method of teaching medicine His suggestion led directly to the development of the Cabot clinical pathological conferences at the Massachusetts General Hospital This method of teaching medical diagnosis was soon taken up in other medical schools

At the Johns Hopkins Medical School clinical pathological conferences were conducted for many years by Dr William S Thayer (clinician) and Dr William G MacCallum (pathologist) After Thayer s death in 1933 the conferences were taken over by Dr Louis Hamman (clinician) and Dr Arnold R Rich (pathologist) Some of these conferences were published in detail in *International Clinics* One or both of us attended many of the conferences held by Drs Thayer and Hamman and since Dr Hamman s death in 1946 the conferences have been conducted by one of us (A McG H) in collaboration with Dr Rich Most of the case material which is to be presented herewith was derived from actual experience in the Wednesday clinical pathological conferences at the Johns Hopkins Medical School A few cases have been selected from similar conferences held by one of us (J B) in collaboration with Dr Clinton van Z Hawn at the Mary Imogene Bassett Hospital Through the courtesy of Dr Charles W Wainwright we have had an opportunity to study many of the detailed discussions prepared by Dr Hamman for his conferences Dr Hamman s former students and colleagues will quickly recognize the fact that his posthumous contribution to this book has been a very considerable one We have drawn freely from the systematic classifications of the various categories of disease which were preserved in his notes or were published during his lifetime For the discussions presented in certain chapters including those on aortic insufficiency heart failure sudden death and pain in the chest we have adhered closely to Dr Hamman s publications relating to these subjects The specific references will be found at the end of each chapter

II

This book attempts to provide a method of approach to the diagnosis of disease It is not a textbook, and it does not presume to deal systematically with the whole field of medical diagnosis It assumes that the reader—medical student or practicing physician—has already acquired the basic information contained in a variety of medical textbooks Through the use of such books and through practical experience the reader will be familiar with history taking physical diagnosis the classification and natural history of diseases and a host of diagnostic tests and procedures Despite his possession of this large body of formal information and practical techniques he will certainly have encountered difficulty in the solution of involved diagnostic problems Such problems usually present themselves as amorphous complexities Most available reference books on the other hand, present their subject matter in logical sequence stripped as far as possible of the complexities that might confuse the student In general they work from the simple toward the complex If there is a section on differential diagnosis it is placed near the end of the chapter The present volume in the consideration of each specific diagnostic problem reverses the usual process by beginning with the complex and working toward the simple It thus simulates the conditions under which the physician must actually work

The ultimate step in differential diagnosis consists in selecting from a number of possibilities the disease or diseases which come nearest to explaining the clinical and laboratory findings in the case in question In leading up to this step one may find assistance in the textbooks that give a list of findings which will help one to distinguish other diseases from the disease in question Or one may turn to the condensed treatises which enumerate in orderly fashion the various diseases which give rise to a particular sign or symptom Neither of these methods of presentation gives an adequate concept of the process of analysis which must be employed in dealing with diagnostic problems This concept can be gained only by repeating over and over again the actual analytic process However it may be acquired more rapidly and made more meaningful if one proceeds along the lines of some well tested plan

In the section to follow the methods and principles of differential diagnosis will be discussed Our purpose is to present this subject as a systematized discipline Too frequently the student looks upon the

process of diagnosis as beginning with a series of shrewd guesses and ending with an effort to bring the facts into line with the guesses He would do better to begin as in all scientific research by marshalling all the facts then proceeding with an unprejudiced analysis of the facts and ending with a logical conclusion

The section on methods and principles is followed by chapters which have no sequential significance In these chapters the reader will be given an opportunity to follow the process of differential diag nosis as it was actually employed by others in clinical pathological conferences The chapter headings represent important signs or symp toms which may be caused by several different diseases Each chapter begins with a brief discussion of the diagnostic implications of the subject followed by the presentation of a series of illustrative cases The discussion of differential diagnosis which follows the case his tories is exactly the same as the one offered at the conference before the correct diagnosis was revealed by the pathologist * In some in stances a much better discussion could be constructed in retrospect This however would circumvent the main purpose of the book which is to enable the reader to develop a sound approach to differ ential diagnosis by observing both the successes and the failures of those experienced in the field

Mention has already been made of Cabot s observation that phy sicians are very suspicious of any attempt to tabulate their methods of reasoning Tabulations are offered in the various chapters with full realization of their deficiencies The field of medicine is changing so rapidly that tables prepared today become outdated within a period of a few months or years For this reason we have not striven to make the tables complete in all details but rather to present them as frames of reference which may serve to orient the physician in the consideration of specific problems The details can be considered complete only after they have been amplified and brought up to date by the physician himself As evidence of the basic validity of the tables it may be said that some of them were originally prepared by Dr Hamman in the early 1930 s Through the intervening years with only slight modifications they have served very satisfactorily to guide differential diagnosis in clinical pathological conferences

In a final chapter a series of cases is presented in a form which will permit the reader to make his own analyses He may then refer

* In some of the case discussions deletions have been made to avoid dupli cation of material presented earlier in the chapter The notes which follow the presentation of the autopsy findings were added in retrospect

to the discussion of the case as it actually took place in the clinical pathological conference Finally the conclusions reached both by the reader and by the discusser may be checked against the autopsy findings

It may be appropriate to say a few words in justification of depending entirely upon material from clinical pathological conferences for the exposition of differential diagnosis It must be admitted that this approach has serious limitations It tends to exaggerate the difficulties of diagnosis and of necessity it prevents consideration of the diagnosis of diseases which do not run a fatal course or in which accurate diagnosis results in the institution of life saving therapeutic measures For teaching certain types of diagnosis the bedside clinic has obvious advantages over the clinical pathological conference This is particularly true when the conclusions reached can be verified or disproved by a surgical operation or by some procedure or test which yields an unequivocal answer

The advantages offered by the clinical pathological conference are principally two (1) by proper selection of case material from the large pathology pool the discussions can be guided into fruitful areas and (2) the validity of the conclusions reached by the clinician can in all cases be judged immediately The value of the conference as an exercise in differential diagnosis depends almost wholly upon the policy which governs the selection of cases If the selection is made by a pathologist who has only a mischievous desire to tease and embarrass his clinical colleagues the exercise loses much of its meaning It is likely to take on the aspect of a quiz program or a guessing contest On the other hand if the clinician has confidence in the pathologist and knows that the case was chosen for the purpose of demonstrating principles and methods in differential diagnosis he can proceed with his discussion confident that care and skill in analysis will be rewarded The Wednesday conferences at the Johns Hopkins Medical School are teaching exercises for medical students rather than staff conferences The clinician who discusses the case is ignorant of the diagnosis but he is not asked to base his discussion on a mere clinical abstract prepared by a third party He is given the complete clinical record in its original state with the raw notes of the students the house officers the nurses the attending physicians and all others who contributed to the record He thus obtains a better appreciation of the total situation as it existed during the patient s life The clinician also examines personally the x ray pictures elec

trocardiograms photographs of important lesions and any other clinical relics which remain from the study of the living patient He then prepares his own abstract Not only is the clinician fully responsible for assembling the raw materials for the conference he must also accept full responsibility for the clinical discussion and final diagnosis No one in the audience is asked to debate the case or offer alternate solutions The clinician has the advantage of knowing the opinions expressed by those who cared for the patient during life He may agree or disagree with these opinions He strives always to reach an unqualified diagnosis but when he believes that the facts do not warrant this he may point out his reasons for so believing and state that to go further would be pure guesswork It is realized that this approach provides a type of clinical pathological conference which is very different from that which is familiar in some other institutions An appreciation of the difference seems essential to an understanding of this book

The fact that the cases for conference were originally selected to illustrate principles in diagnosis rather than blunders in diagnosis accounts in part for the high percentage of correct diagnoses The percentage was further increased by deletion from our material of those cases in which because of inadequate or inaccurate factual data the clinician s entire discussion was based upon a false premise and could therefore only lead to erroneous conclusions Such discussions in retrospect are wholly irrelevant and have no place in this volume

III

Diagnosis involves two procedures (1) collecting the facts and (2) analyzing the facts Errors in diagnosis may be due to imperfect performance of either of these procedures When the factual data are inadequate or incorrect or when they have been misinterpreted the analysis though faultless in itself will lead to an erroneous conclusion On the other hand when the collection of facts has been complete and accurate and when the data have been correctly interpreted the conclusions may be in error because of faulty analysis The following outline presents the successive steps which lead up to *the diagnosis This volume will be concerned chiefly with the analysis*

of the facts A few introductory remarks will be made concerning collection of the facts

Steps in Diagnosis

1 Collecting the Facts

- (a) Clinical history
- (b) Physical examination
- (c) Ancillary examinations
- (d) Observation of the course of the illness

2 Analyzing the Facts

- (a) Critically evaluate the collected data
- (b) List reliable findings in order of apparent importance
- (c) Select one or preferably two or three central features
- (d) List diseases in which these central features are encountered
- (e) Reach final diagnosis by selecting from the listed diseases either (1) the single disease which best explains all the facts or if this is not possible (2) the several diseases each of which best explains some of the facts
- (f) Review all the evidence—both positive and negative—with the final diagnosis in mind

The facts for differential diagnosis come from four sources (1) clinical history (2) physical examination (3) ancillary examinations involving special techniques and laboratory methods and (4) observations of the course of the illness The history must be taken with care and it must be evaluated with due regard to its reliability The patient s account of his symptoms is limited by his mental competence and by his powers of observation and description It is usually colored by his fears and by his confidence in and reaction to the physician The historian should always record his evaluation of the reliability of the history and facts which are considered doubtful should be corroborated and amplified by those who have known the patient Some seemingly trivial event in the history once brought to light and properly evaluated may hold the key to the correct diagnosis Similarly the physical examination must be conducted with thoroughness and with alertness to detect even slight deviations from normal The recorder should make a clear distinction between unequivocal and questionable observations

The history and physical examination provide the essential basic facts for diagnosis Facts obtained by other means may be superfluous or even misleading The current use of laboratory methods on a large scale in the teaching medical centers has tended to exaggerate the importance of these techniques in the analysis of clinical problems Slight deviations in chemical measurements scarcely beyond

the limits of error of the method employed may be greatly overemphasized in their relation to the clinical facts A blood culture an x ray picture an electrocardiogram or a blood chemistry determination may clarify obscurities and provide information which is indispensable for accurate diagnosis But when the results of such tests cannot be correlated with the facts disclosed by the history and physical examination they should be considered subsidiary to the main issue In spite of the crucial significance of the ancillary examinations in many cases it seems important to emphasize that skill in differential diagnosis is not determined by one s ability to assemble and correlate laboratory reports

The fourth body of facts contributing to the diagnosis is that provided by observation of the course of the illness as it unfolds before the physician The observer must avoid the temptation to make these facts fit into his earlier conception of the diagnosis He must view them with an open mind and be willing to change his opinions in the light of the new developments Frequent progress notes recording observations and outlining thoughts about the case from time to time provide a valuable source of information The correct diagnosis may be possible only at a later date when the progress notes are reviewed together with all other pertinent data

The physician who is called upon to analyze the facts may find himself in the position of a drama critic who is asked to render an opinion about a play after having been permitted to see only the third of four acts He may be able to learn something about the first two acts from other relatively unobservant and technically inexperienced members of the audience who actually saw those acts But the fourth act has yet to be performed The wise critic would of course withhold his opinion unless he was permitted to see the play through from beginning to end The physician however despite his limited view may not arbitrarily withhold his opinion He is dealing with matters of life and death and he has been trained to render his opinion at any stage of the play He may do this with safety only if he and those who have sought his views are fully aware that opinions based on limited information are tentative they become final and conclusive only after all the necessary information is at hand

The physician must therefore begin his analysis of the facts not only by determining their reliability and intrinsic significance but by considering their relation to the patient s total illness For example a negative agglutination test for a specific organism may be of no significance early in the illness but assume great significance at a later

stage Critical evaluation of various physical findings and laboratory tests requires a knowledge of the natural history of diseases as well as of the manifestations which are to be evaluated

In listing the findings it is helpful to arrange them in order of apparent importance and to underscore those which should be accounted for by the final diagnosis The beginner in the study of differential diagnosis has particular difficulty in separating the wheat from the chaff He may overrate the significance of some finding and be led by it up a blind alley Minor elevations in blood pressure slight deviations in electrocardiographic tracings insignificant shadows in x ray films may be accorded falsely high values Only through repeated successes and failures does one acquire the ability to arrange the facts in proper perspective The evaluation of the relative significance of the findings is one of the aspects of the process of analysis which is best learned through the experience of clinical pathological conferences At the end of the conference one may always go back to the original list of findings and determine the point at which misplaced emphasis led the analysis astray The case discussions in the various chapters are repeatedly concerned with the problem of distinguishing between significant and insignificant facts

The facts may first be listed in the order in which they appear in the clinical record as in the example which follows

Abdominal pain
Vomiting
Tachycardia
Slight enlargement of submaxillary and inguinal lymph nodes
Hepatomegaly
Generalized abdominal distention and tenderness
Ascites
Right inguinal hernia
Right varicocele
Hemorrhoids—external and internal
Absence of right great toe
Hypoactive knee jerks
Albuminuria—slight
Anemia—hypochromic—slight
Hyperglobulinemia
Hyperbilirubinemia—predominantly direct reaction
Elevated serum alkaline phosphatase

Before these findings can be arranged in order of importance each one must be considered and evaluated separately For example if the absence of the great toe was due to a traumatic amputation 25 years previously it would be relegated to a position near the bottom of the list On the other hand if the toe had been amputated only 6

months previously because of an expanding pigmented mole it would be placed near the top of the list Similarly the importance attached to the hernia would depend on whether it was irreducible or exhibited evidences of strangulation Findings such as slightly enlarged lymph nodes hypoactive knee jerks and hemorrhoids are encountered in many healthy people and rarely deserve a prominent position in the initial listing Tachycardia slight anemia and slight albuminuria are non specific accompaniments of many diseases and would be placed low on the list unless there were particular reasons for placing them higher After careful consideration of all the findings they should be relisted in order of importance which might be as follows

<u>Hepatomegaly</u>
<u>Jaundice</u>
<u>Ascites</u>
<u>Abdominal pain and tenderness</u>
<u>Vomiting</u>
<u>Hyperbilirubinemia—direct reaction</u>
<u>Elevated serum alkaline phosphatase</u>
<u>Hyperglobulinemia</u>
Slightly enlarged lymph nodes
Right inguinal hernia
Hemorrhoids
Tachycardia
Albuminuria
Anemia
Right varicocele
Hypoactive knee jerks
Absence of right great toe

The first eight items have been underscored as the items which should be accounted for by the diagnosis As emphasized earlier some of the items which are placed low in the initial listing may assume greater significance at a later stage in the analysis For example the hemorrho ds might weigh the balance in favor of portal obstruction

After the facts have been critically evaluated and listed in the order of apparent importance one may find on the list some fact which in itself determines the primary diagnosis An example of this would be the Kayser Fleischer ring which is pathognomonic of Wilson s disease If all the other items on the list are adequately explained by a diagnosis of Wilson s disease the analysis need proceed no further However one usually finds that the facts which have been listed are common to several diseases It then becomes desirable to select some

outstanding feature to orient the analysis Examples of such central or orienting features are fever, jaundice anemia hepatomegaly, ascites gastrointestinal hemorrhage, renal failure and heart failure It is best to select a feature which is objective, preferably one which may be at least roughly quantitated In some cases subjective complaints, such as pain in a particular anatomical area, may dominate the picture and constitute the only feature serving to orient the analysis The selection of a central feature which will guide the analysis along a productive course requires practice and an understanding of the natural history and hallmarks of a wide variety of diseases

When the case presents two or more features which appear to have the same potential value it is best not to base the analysis on only one of them Two or more analyses may be made, each based upon one of the features In this way it may be possible to find two avenues which lead to the same diagnosis

For each feature selected one should list the diseases and conditions which may account for its presence Many detailed examples of this process will be found in the case discussions To illustrate the principle one may cite a recent difficult problem in differential diagnosis which was successfully solved The patient had a large liver renal insufficiency and signs of heart failure Analysis involved the listing of the possible causes of each of these three features The evidence indicated that the cause of the cardiac failure was myocardial disease and the list of myocardial diseases leading to failure included amyloidosis Amyloidosis also appeared on the lists of diseases giving rise to hepatomegaly and renal insufficiency Thus amyloidosis was high on the list of conditions which could account for all three features Initially it seemed more probable that the hepatomegaly and renal insufficiency were due to chronic passive congestion secondary to the heart failure However the chronic passive congestion subsided under appropriate treatment whereas the hepatomegaly and renal insufficiency remained unaffected A review of the facts at this stage of the analysis indicated that amyloidosis was the one disease appearing on the lists which could satisfactorily explain all of the findings Although amyloidosis was the final diagnosis at the time of the clinical pathological conference this diagnosis had not been seriously entertained prior to the patient s death This failure was due in large part to lack of systematic analysis of the type employed at the conference

In the case just cited the fatal outcome would not have been prevented even if a correct diagnosis had been made during life But

experience in clinical pathological conferences indicates that in some instances adequate analysis of the facts during the patient s life might have resulted in the institution of life saving therapy One recalls for example a case of empyema mistaken for an inoperable carcinoma of the lung constrictive pericarditis mistaken for cirrhosis of the liver syphilitic gumma mistaken for a malignant tumor and pheochromo cytoma in a patient believed to have severe essential hypertension In all of these cases the correct diagnosis might have been entertained early enough for institution of successful treatment if only the facts had been subjected to systematic analysis Admittedly such analysis is more difficult during the patient s life than it is after the illness has run its full course and the accumulated facts can be studied with calm detachment This however is not a satisfactory explanation of all the clinical failures for in many of them it is obvious that if the data had been analyzed systematically at intervals during the illness the cor rect diagnosis could hardly have been overlooked

Experience has shown that it is desirable always to attempt to ex plain all of the manifestations of an illness on the basis of a single disease An example in which adherence to this principle led to a correct analysis of the problem is the following A young woman who unquestionably had scleroderma also had arthritis of multiple joints cardiac failure hypertension and encephalopathy and died follow ing a gastrointestinal hemorrhage After all of these manifestations had been evaluated it was concluded that they could all be explained on the basis of diffuse scleroderma This proved to be the case The encephalopathy was due to collagen disease of the cerebral arteries The hemorrhage had arisen in an area of ulceration in the esophagus which showed changes typical of scleroderma Multiple diagnoses were entertained in this case until there was a deliberate effort to find a single explanation of all of the findings Needless to say such efforts must be based on a broad knowledge of the many ways in which a disease such as scleroderma may manifest itself

In the effort to find a single etiological explanation for the findings one must take a realistic and unbiased look at all of the facts other wise one may be blinded to the characteristic evidences of a second complicating disease process Such a case was that of a boy with sickle cell anemia with pain in the right lower quadrant of the ab domen In an attempt to explain all of the findings on a single basis it was concluded that the abdominal pain was due to a hemolytic crisis Actually the collateral evidences of a crisis had never been adequately investigated while the characteristic features of acute ap

pendicitis were overlooked The correct diagnosis was not made until the appendix had ruptured and peritonitis had set in In this case the desire to attribute everything to the sickle cell anemia had kept the physician from taking an unbiased look at the facts

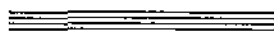
In any effort to decide which of several alternate diagnoses is the correct one the element of probability must be considered Probability is always in favor of the most common disease which will furnish a satisfactory explanation of all the findings For example by far the most common cause of mitral stenosis is rheumatic endocarditis If the physician made a diagnosis of rheumatic endocarditis in every case of mitral stenosis he would be right in more than nine out of ten cases It is important always to think first of the common disease However in every case before arriving at a final diagnosis one must be fully satisfied that the common disease explains *all* of the findings If the patient with mitral stenosis has in addition an enlarged spleen and petechiae obviously one is no longer concerned with the commonest cause of mitral stenosis the interest shifts to the commonest cause of the triad mitral stenosis splenomegaly and petechiae One should therefore think of probabilities only in terms of the total picture

The last step in the analysis consists in going back to the list of findings and reconsidering each in the light of the diagnosis or diagnoses which seem most probable Does one diagnosis account for all of the underscored items? If so which of the subsidiary items are not accounted for? Are these items significant or may they be discounted as normal variations? Is it necessary to make two diagnoses to account for all of the underscored items or to account for the significant subsidiary items which cannot be explained by the primary diagnosis? At this stage of the analysis attention must also be given to negative findings Does a negative cold agglutination test exclude the diagnosis of primary atypical pneumonia? What value may be attached to a negative serologic test for syphilis when the other findings point to a diagnosis of syphilitic aortitis?

The weighing of all the positive and negative evidence bearing upon the possible diagnoses receives particular attention in the following chapter

In order to avoid repetition and to conserve space the procedures involved in differential diagnosis are presented in full in only the first case in Chapter I In the other cases the reader must assume that the findings have been evaluated and listed The recorded discussion has

for the most part been reduced to analysis of the facts and weighing of the evidence for or against various possible diagnoses



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Chapter 1

AORTIC INSUFFICIENCY

AORTIC INSUFFICIENCY when fully developed is easily recognized The clinical diagnosis depends upon the presence of a diastolic murmur of peculiar quality and position associated with characteristic changes in the peripheral circulation the most striking being an increase in the visible and palpable arterial pulsations exemplified by the so called Corrigan pulse Neither of these cardinal signs is in itself conclusive evidence of aortic insufficiency A murmur *similar in quality and location may be heard in patients having mitral* stenosis pulmonic insufficiency or certain congenital cardiac defects Peripheral manifestations which are likewise indistinguishable from those of aortic insufficiency may be observed in patients who have hyperthyroidism a considerably elevated body temperature or an arteriovenous aneurysm

Although the combination of the characteristic murmur with the characteristic peripheral signs is usually indicative of aortic insufficiency exceptions must be kept in mind An exceptional case of this type which had deceived a number of experts was correctly diagnosed when subjected to more searching and systematic consideration in preparation for a clinical pathological conference (Hamman and Rich 1933) The patient a man aged 49 years had been under close observation in the hospital for many weeks Throughout this period he had had an enlarged spleen and a variable fever and many blood cultures were positive for *Streptococcus viridans* All observers agreed that the diastolic murmur heard along the left border of the sternum was characteristic of aortic insufficiency On the other hand the peripheral signs of aortic insufficiency were noted by only a few observers and were never convincing No one doubted that the patient had subacute bacterial endocarditis and without giving due consideration to the alternatives everyone concluded that the vegetations

were on the aortic cusps In preparing this case for conference Dr Hamman was impressed by the absence of peripheral emboli during the long period of careful observation On the other hand there had been several episodes which were interpreted as being due to pulmonary infarction It was reasoned that the variable peripheral signs might have been accounted for by the variable fever and were therefore not acceptable evidence of aortic valvular disease Since the pulmonary infarcts were presumably produced by emboli from the right side of the heart it was correctly deduced that the murmur was due to pulmonic rather than aortic insufficiency The correct diagnosis in this instance depended in part upon the equivocal character of the peripheral manifestations of aortic insufficiency but in greater part upon the location of the emboli This case is cited to emphasize the facts that a murmur indistinguishable from that of aortic insufficiency may be caused by other valvular lesions and that all of the evidence must be carefully sifted and the site of the anatomic defect correctly placed before one proceeds to a consideration of its etiology Further discussion of this point will be found in the case histories

In the cases which will be discussed in the remainder of this chapter we shall assume that the diagnosis of aortic insufficiency has been made with certainty The most common causes of such a lesion are rheumatic fever and syphilis however cases will be found which fall into the following* eight categories

(1) Rheumatic aortic insufficiency
(2) Syphilitic aortic insufficiency
(3) Bacterial aortic insufficiency
(4) Calcific aortic stenosis and insufficiency
(5) Congenital defects with aortic insufficiency
(6) Arteriosclerotic aortic insufficiency
(7) Relative aortic insufficiency
(8) Traumatic aortic insufficiency

Each of these categories will be considered separately with view to determining characteristic features which should aid in making a satisfactory differentiation

RHEUMATIC AORTIC INSUFFICIENCY

Age of Onset Rheumatic fever is primarily a disease of young people The first attack seldom occurs after the age of 20 years

* This classification is that proposed by Dr Louis Hamman and the discussion which follows is based largely on his Roger Morris Lecture given in Cincinnati in May 1944

SYPHILITIC AORTIC INSUFFICIENCY

AGE OF ONSET Syphilitic aortic insufficiency is first observed between the ages of 30 and 60 years in at least 80 per cent of the cases However there is a definite relation between the age at which syphilis is acquired and the age at which the cardiac symptoms appear the earlier the acquisition of the disease the earlier the development of the aortic lesion The occasional cases of syphilitic aortic insufficiency which have been observed in patients under the age of 20 years are usually attributable to a primary infection acquired before the age of 10 years

CLINICAL COURSE Once symptoms have developed in a case of syphilitic aortic insufficiency they progress with fewer, less complete and less prolonged intermissions than those which characterize the course of rheumatic heart disease The earliest symptoms may be in the form of sudden paroxysms of dyspnea which occur particularly at night Auricular fibrillation which is common in cases of rheumatic heart disease is rare in cases of syphilitic aortic insufficiency The duration of life after the discovery of the valvular defect varies somewhat from case to case and depends to some extent upon the type of treatment employed but it rarely exceeds two or three years

INVOLVEMENT OF OTHER HEART VALVES Signs of aortic stenosis common in cases of rheumatic or calcific aortic insufficiency *are rarely encountered in cases of syphilitic etiology* As *mentioned* above syphilitic aortic insufficiency may be accompanied by the auscultatory signs of mitral disease in the absence of anatomical deformity of the mitral valve Organic disease of the mitral or other valves not attributable to the syphilitic infection may occasionally be encountered as an incidental finding

DILATATION OF THE AORTA Dilatation of the aorta is a characteristic although not an invariable feature of syphilitic aortitis It is usually localized in the ascending aorta and may lead to the development of a true aneurysm In cases of aortic insufficiency of doubtful origin dilatation of the aorta should weigh the evidence in favor of a syphilitic etiology *However disease other than syphilis* may lead to aortic dilatation Roentgenographic disclosure of extensive calcification of the wall of the dilated aorta does not rule out the presence of syphilis as this finding is frequent in patients with aortic syphilis

EVIDENCE OF SYPHILITIC INFECTION Repeatedly positive serologic tests for syphilis may be considered as evidence of syphilitic infection but since syphilis may be acquired by individuals who have

rheumatic and other forms of heart disease the significance of the positive tests must be weighed with all the other evidence Biological false positive tests may confuse the issue and in all questionable cases particularly *if a history of primary or secondary syphilitic manifesta tions* is lacking the serologic test should be viewed with suspicion unless it is confirmed by the treponemal immobilization test of Nelson and his co workers Repeatedly negative serologic tests occur in a small percentage of cases of syphilitic aortic insufficiency

BACTERIAL AORTIC INSUFFICIENCY

Cases of bacterial endocarditis present a twofold diagnostic prob lem owing to the fact that the vegetations are usually implanted on previously deformed or anomalous structures The primary problem is to establish the presence of the bacterial infection the secondary problem is to determine the etiology of any underlying lesion The so ution of the second problem is less imperative in the case of aortic valve lesions than in those conditions which may be more amenable to surgical treatment after the bacterial infection has been eradicated But even in the case of aortic valve lesions it is of considerable prog nostic importance to know whether the underlying condition is the common rheumatic deformity the less common congenital anomalies or syphilitic aortic disease which serves relatively uncommonly as a foundation for bacterial vegetations Once the bacterial infection has been eradicated the prognosis is determined in part by the natural course of the underlying disease and in part by the deformities which have resulted from the destructive and reparative processes of the superimposed bacterial disease

The acute forms of bacterial endocarditis due to the hemolytic streptococcus or pneumococcus may be distinguished by the ful minant character of the illness It is in this group of cases particularly that vegetations are likely to develop on normal aortic cusps The signs of aortic insufficiency may not be present when the patient first comes under observation and may even make their first appearance while the patient is convalescing from the acute phase of the illness In some cases the evidence of valvular disease may be misinterpreted or overlooked owing to preoccupation with some more spectacular manifestation of the infection such as meningitis

The subacute and chronic forms of bacterial endocarditis may occur with such mild and atypical symptoms that the correct diagnosis is never even considered *One s suspicion should be aroused in all cases* of valvular disease when fever or anemia is present The suspicion

should become acute if the patient gives a history of having had a recent surgical operation dental extraction or localized or generalized infection. An accurate diagnosis may be made in a high percentage of cases if the patient is examined at frequent intervals for petechiae for changes in the quality of the cardiac murmurs, and for the other well known evidences of bacterial endocarditis together with persistent efforts to cultivate organisms from the blood In recent years there has been a growing tendency to treat low grade fevers of obscure origin including unrecognized cases of bacterial endocarditis with short courses of penicillin or other antibiotic agents Such treatment may bring about a temporary improvement in the symptoms but it adds materially to the difficulty in arriving at an accurate diagnosis If bacterial endocarditis has been treated with inadequate amounts of antibiotics it becomes extremely difficult and at times impossible to obtain positive blood cultures even when the continued progress of the disease may be made manifest by such serious complications as embolic phenomena and gradual renal failure

CALCIFIC AORTIC STENOSIS AND INSUFFICIENCY

Calcific aortic stenosis and insufficiency are encountered usually in persons over the age of 50 years The cause of the calcific deposits is not always clear and it is probably not always the same In some cases the initial deposits appear to have occurred at the site of healed bacterial lesions In others the clinical course would seem to indicate that the changes have resulted from slowly progressive degenerative disease although the lesions may not resemble those of arteriosclerosis In cases of calcific aortic insufficiency the signs of aortic stenosis almost invariably predominate The conspicuous auscultatory sign is a rough aortic systolic murmur transmitted into the neck vessels This murmur is frequently accompanied by a thrill which may also be felt over the vessels at the base of the neck Careful x ray examination of the valvular area for the presence of calcium deposits will usually establish the diagnosis in this type of aortic insufficiency

CONGENITAL DEFECTS WITH AORTIC INSUFFICIENCY

The distinction between acquired disease and congenital defects may at times be difficult In some cases such a distinction is impossible since the acquired lesions have been engrafted upon congenital anomalies Most of these anomalies are rare The commonest con

genital defects associated with signs of aortic insufficiency are (1) subaortic stenosis in which aortic insufficiency may be a late development and the predominating signs are always those of stenosis and (2) the Eisenmenger complex in which the dextroposition of the aorta and the high septal defect result in the production of an intense and widely *transmitted systolic murmur and thrill* *The roentgenographic* findings may be of considerable assistance in distinguishing these congenital anomalies Two rare but interesting conditions associated with signs of aortic insufficiency are (1) the type of congenital aortic dilatation encountered in some cases of arachnodactyly and (2) aneurysm of the sinus of Valsalva rupturing into the right ventricle The latter condition which may be of syphilitic or mycotic as well as of congenital origin does not represent a true aortic insufficiency although it is accompanied by the characteristic auscultatory and peripheral signs Except in the cases of mycotic origin the patient is usually in excellent health until the rupture of the aneurysm is signaled by the sudden development of acute and progressive dyspnea

ARTERIOSCLEROTIC AORTIC INSUFFICIENCY

Arteriosclerotic aortic insufficiency is a rare condition even in patients over 50 years of age. Occasionally an arteriosclerotic plaque will encroach upon the valve in one of the sinuses of Valsalva gradually distorting it to produce some degree of insufficiency Generally when this diagnosis is entertained it proves to be erroneous since the condition is of such very rare occurrence

RELATIVE AORTIC INSUFFICIENCY

Relative aortic insufficiency occurs when there is enough dilatation of the aortic ring to prevent approximation of the edges of the cusps The insufficiency is usually of slight degree and is accompanied by an evanescent faint diastolic murmur without the characteristic changes in the peripheral circulation Occasionally the defect is of greater magnitude and is accompanied by all of the signs of fully developed aortic insufficiency Relative aortic insufficiency is attributable most commonly to one of three conditions (1) a greatly increased arterial blood pressure, (2) arteriosclerotic syphilitic or other changes in the aorta leading to dilatation or (3) dissecting aneurysm When relative aortic insufficiency occurs in association with hypertension it is usually late in the course of the disease and there is rarely any significant indication in the peripheral circulation

When associated with dissecting aneurysm the evidences of aortic insufficiency may be quite dramatic The sudden occurrence of outspoken signs of aortic insufficiency in a case of long standing hypertension should lead one to suspect the development of dissecting aneurysm

TRAUMATIC AORTIC INSUFFICIENCY

Traumatic aortic insufficiency is a rare condition seen usually after trauma which has caused sudden extension of the head and neck

Under this heading it might be appropriate to consider the cases in which aortic insufficiency is due to the rupture of an aortic cusp This occurs almost invariably in valves which are already diseased, and is only rarely associated with trauma The commonest lesion preceding the rupture is bacterial endocarditis This type of aortic insufficiency has been observed more frequently since the advent of the effective antibiotic agents Valves which have been greatly weakened or almost completely dissolved during the stage of bacterial invasion may develop fenestrations at times or rupture either during the acute phase of the illness or during convalescence Such events are usually followed by the development of acute heart failure

Illustrative Cases

I

(#384084 Admitted May 2 1946 Died June 2 1946)

THIS 51 year old white electrician complained of extreme shortness of breath There was no history suggestive of rheumatic fever or syphilis but he had been told at the age of seven that he had a leaky heart One year before admission he had his first episode of shortness of breath while walking to work He was examined by the plant physician who again told him that he had a leaky heart Six months later he remained home for five or six weeks with severe dyspnea and orthopnea but had no edema or precordial pain Following this he was able to return to work but missed an occasional day when his dyspnea was severe One week before admission the dyspnea and orthopnea returned with increasing severity It was stated that he had had several bouts of severe substernal pain each of short duration but no information was available about the character of the pain

PHYSICAL EXAMINATION *on admission* T 99 6 P 84 *apical* 80 radial R 22 B P 140/45

The patient was intensely cyanotic disoriented restless and markedly dyspneic and orthopneic There was some arteriosclerosis of the retinal vessels Fine and medium rales were present at both lung bases posteriorly Cardiac dullness extended 13 5 cm to the left in the 5th interspace and 7 cm to the left in the 1st interspace with definite increase in retro manubrial dullness There was a palpable systolic thrill at the apex The cardiac impulse was diffusely visible over the 4th to 6th interspaces The rhythm was grossly irregular and there were numerous coupled beats A blowing systolic apical murmur was heard transmitted to the axilla A low pitched diastolic murmur with a presystolic accentuation was present over the mitral area There were blowing systolic and diastolic murmurs in the aortic area with transmission of the diastolic murmur down the left sternal border The peripheral pulses were collapsing in quality The liver was 5 fingerbreadths below the costal margin The right leg was obviously larger than the left and there was a positive Homan s sign with calf tenderness A thrombosed superficial vein could be felt running from the right knee up to the right inguinal area Reflexes were equal and active

COURSE IN THE HOSPITAL The patient was digitalized given oxygen and sedatives and phlebotomy was done with the removal of 500 cc of blood With this treatment his condition improved greatly Because of the

elevation in the temperature he was placed on penicillin Fever disappeared for a short while but rose again on May 5 and remained between 100 and 103 thereafter gradually falling again to normal limits at the end of the second week in the hospital On May 10 he was started on quinidine and three days later had a normal sinus rhythm At this time he had precordial pain with coldness and cyanosis of the extremities Following this he seemed improved but two days later auricular fibrillation again became evident On May 22 evidences of peripheral edema first appeared During the second week of his stay in the hospital a pleural friction rub was noted over the anterior chest on the right side During the last few days of his life the extremities were cold and clammy

ANCILLARY FINDINGS Blood serologic test for syphilis positive 24 units Venous pressure 270 mm of water on admission 120 mm of water on May 4 Circulation time 55 sec Chemical examinations of the blood nonprotein nitrogen 57 mg % chloride 90 9 mEq CO_2-combining power 27 mEq total serum bilirubin 1 3 mg % Blood cultures May 11 13 19 showed no growth Electrocardiogram showed left axis deviation with auricular fibrillation May 12 the electrocardiographic examination showed normal sinus rhythm with P R interval of 0 16 to 0 18 sec with left axis deviation X ray examination May 6 showed extensive infiltrative changes in both upper lung fields compatible with congestive change or an acute pneumonic process May 20 x ray of chest heart markedly enlarged aorta dilated and tortuous calcium in the walls Lungs clear Vascular markings prominent

DISCUSSION OF FINDINGS The findings may be listed as follows

From History

Leaky heart at age 7 years
Dyspnea for one year
Orthopnea
Substernal pain

From physical examination

Cyanosis
Dyspnea
Rales at lung bases
Enlarged heart
Totally irregular cardiac rhythm
Systolic and diastolic murmurs at apex
Systolic and diastolic murmurs in aortic area
Hepatomegaly
Venous thrombosis and edema right leg

From ancillary examinations

Positive serologic test for syphilis
Increased venous pressure
Electrocardiogram auricular fibrillation and left axis deviation

X ray Enlarged heart dilated tortuous aorta with calcific deposits in wall infiltrative changes both lungs
Slight elevation in blood nonprotein nitrogen with hypochloremia

From course of illness

Variable fever
Temporary reversion to normal sinus rhythm
Transitory episode of precordial pain
Peripheral edema
Pleural friction rub

Combining some of the findings and re arranging them in order of apparent importance

Enlarged heart
Auricular fibrillation
Murmurs in aortic area
Murmurs at apex
Dilated and tortuous aorta
Dyspnea and orthopnea
Edema
Increased venous pressure
Hepatomegaly
Cyanosis
Rales at lung bases
Positive serologic test for syphilis
Venous thrombosis right leg
Substernal pain
Pleural friction rub
Fever
Slight nitrogen retention
Hypochloremia

All of these findings seem important with the possible exception of the last two

In beginning the diagnostic analysis it was accepted that many of the findings were attributable to cardiac failure This feature might have been chosen to orient the analysis (Analyses based on this feature will be found in a subsequent chapter) However in the present case it was decided that the analysis would be more productive if aortic insufficiency were chosen as the orienting feature

Discussion of Differential Diagnosis Aortic insufficiency was accepted as the orienting feature in this case because there appeared to be no doubt about this lesion The presence of a diastolic murmur of characteristic quality and in the typical location combined with a collapsing pulse and conspicuous visible pulsations in the peripheral arteries led to the assumption that whatever other

cardiac lesion there might be aortic insufficiency was certainly present

Whether there was also a mitral valve lesion cannot be decided so readily This would be an important matter to determine particularly if the decision were an affirmative one for then it could be concluded without hesitation that the patient had rheumatic disease of the heart However, it is exceedingly difficult to make a clinical diagnosis of mitral stenosis when fully developed aortic insufficiency is present Experience in these clinical pathological conferences has shown that when mitral stenosis is found at autopsy it has almost uniformly been predicted clinically On the other hand in many instances a clinical diagnosis of mitral stenosis has not been confirmed at autopsy Almost invariably this error has been attributable to the presence of aortic insufficiency The so called Flint murmur heard in free aortic insufficiency may have auscultatory characteristics which are precisely the same as those of the presystolic rumble of mitral stenosis The location may also be the same and the murmur may be accompanied by a presystolic thrill So, in the presence of aortic insufficiency there must be other signs of mitral stenosis in addition to the typical murmur to justify the diagnosis Such additional signs are a snapping mitral first sound an accentuated pulmonic second sound, exaggeration of the second curve to the left in the cardiac shadow fluoroscopic evidence of dilatation of the left auricle right axis deviation and large P waves in the electrocardiogram None of these collateral signs was present The typical small pulse of mitral stenosis is of course obscured by the collapsing pulse of aortic insufficiency

Since the etiology of the aortic insufficiency cannot be determined by direct examination of the heart one must turn to the associated clinical information Many of the associated findings in this case seem to point toward a syphilitic etiology The serologic test for syphilis was strongly positive The aorta was conspicuously dilated The clinical course was one of steadily downhill progression death coming about one year after the appearance of the first symptoms In rheumatic aortic insufficiency the course is usually characterized by episodes of failure separated by relatively long intervals of good compensation An additional finding this time a negative one weighing the scales in favor of a syphilitic etiology was the absence of evidence of aortic stenosis

The associated findings in favor of a rheumatic etiology were the history of a leaky heart first noted at the age of 7 years and the

presence of auricular fibrillation Not only is this arrhythmia more common in rheumatic than in syphilitic heart disease but it is also more common in the presence of mitral stenosis than with aortic insufficiency alone

Aortic insufficiency due to bacterial endocarditis has little in its favor There were no systemic emboli no splenomegaly no clubbing of the digits and several blood cultures were sterile The pulmonary lesions might have been due to emboli but if the emboli came from bacterial vegetations these must have been located in the right side of the heart There were no signs of tricuspid or pulmonic valve involvement Clinically unrecognized tricuspid lesions are relatively frequent in rheumatic disease but it would be very peculiar to have bacterial lesions confined to the right side of the heart when the diseased valves of the left side of the heart appeared to provide such fertile ground for their development Another argument against bacterial endocarditis is contained in the clinical dictum (which is by no means absolute) that bacterial vegetations are less likely to occur in the presence of severe valve damage with marked cardiac failure and auricular fibrillation than in compensated hearts with minimal valve lesions

Free aortic insufficiency without aortic stenosis is not caused by congenital cardiovascular disease alone although it may result from bacterial implants on a congenitally bicuspid valve The only feature which would give rise to the question of a congenital etiology is the record of a leaky heart at the age of seven years There are so many reasons to doubt a congenital lesion in this case that the early observation of a murmur if reliable is considered to be more in favor of rheumatic heart disease

There was no history to suggest a traumatic aortic insufficiency and the signs and symptoms were unlike those encountered in cases of calcific or arteriosclerotic disease

The precordial pain was not a very prominent symptom It may have been associated with the deficit in coronary circulation which accompanies the low diastolic blood pressure resulting from aortic insufficiency There were no clinical or electrocardiographic features suggestive of myocardial infarction

It is now desirable to give consideration to the fever which was higher and more sustained than one usually sees in congestive heart failure alone and to the attacks of dyspnea with shocklike features and pleural friction rub Pulmonary infarction seems to be a logical explanation of these manifestations In heart disease pulmonary

infarction may be due to an embolus which in this case might have come from

(1) Mural thrombi
(2) Thrombi in the veins of the right leg
(3) Bacterial vegetations on the heart valves

Pulmonary infarction resulting from an embolus formed inside the heart chamber occurs most commonly in cases of mitral stenosis particularly when auricular fibrillation is present These conditions promote thrombus formation in the auricles Detachment of thrombi is favored when the rhythm changes from auricular fibrillation to a normal sinus mechanism In the present case thoracic pain dyspnea and shocklike features developed after a normal sinus rhythm had been temporarily induced by quinidine therapy One might reconstruct the course of the present illness by postulating that the patient s first symptoms of cardiac failure arose when auricular fibrillation with its added mechanical strain first occurred Auricular fibrillation may come in paroxysms for a period of time before it becomes persistent and this man may have had a series of pulmonary emboli during periods of changing rhythm

Thrombosis of peripheral veins is not uncommon in chronic cardiac disease particularly when congestive failure develops Since there were obvious venous thrombi in the right leg of this patient these may have been the source of pulmonary emboli However it is worth noting that there were overt signs of phlebitis and that emboli are more likely to be released in cases of occult phlebothrombosis than when overt phlebitis is present

The evidence indicating that emboli did not come from bacterial vegetations has already been cited

CONCLUSIONS From this discussion one may see that it has not been possible to account satisfactoril for al of the findings on the basis of a single etiologic diagnosis The two etiologic diagnoses which seem most likely are chronic rheumatic heart disease and syphilitic cardiovascular disease In favor of the former are the presence of auricular fibrillation the record of a leaky heart in childhood and the fact that every clinician who examined this patient s heart believed that there was mitral stenosis as well as aortic insufficiency Since we did not examine the patient and therefore cannot be aware of all of the factors which entered into the formation of this unanimous opinion we should have serious reservations about disregarding it In favor of a syphilitic etiology are the strongly positive serologic test for syphilis the dilatation of the aorta the absence of evidences

of aortic stenosis and the rapidly progressive course after the first signs of failure appeared

If it were necessary to decide upon a single etiologic diagnosis syphilis would be the first choice The diagnosis of a leaky heart in childhood might have been based on a functional murmur so common in that age period as a result of anemia fever and other factors Auricular fibrillation does occasionally result from syphilitic heart disease

In rare instances one sees patients in whom there is both rheumatic disease of the mitral valve and syphilitic disease of the aorta and aortic valve Such might be the case here It would then be possible to offer a better explanation of all the findings

ANATOMICAL DIAGNOSIS (Autopsy No 19985) Syphilitic aortitis and valvulitis saccular dilatation of ascending aorta aortic insufficiency Chronic rheumatic endocarditis of mitral valve Mitral stenosis and insufficiency Old organized fibrinous pericarditis Cardiac hypertrophy and dilatation Acute focal interstitial myocarditis Chronic passive congestion of liver and lungs Marked arteriosclerosis of aorta Adrenal cortical adenoma (bilateral) History of thrombosis of vessels of right leg Organizing thrombus in pulmonary vessel

The heart was discovered to be greatly enlarged The epicardium was thickened and opaque The right side of the heart was hypertrophied and dilated The mitral valve was thickened at its free margin and its chordae tendineae were short and thick The left ventricle was hypertrophied and greatly dilated There was sclerosis at the base of the aortic valve and rolling and shortening of both the right and left cusps with flattening and separation of the commissures There was great dilatation of the ascending aorta with roughening wrinkling and plaques of calcification Where the process began just above the sinus and where it encroached upon the coronary orifices it seemed to be syphilitic with superimposed arteriosclerosis

Microscopically the changes in the aorta were extreme with destruction of media and with vascularization and round cell infiltration There were also thickening of the adventitia and narrowing and inflammation about the blood vessels This change was undoubtedly syphilitic The changes in the *mitral valve and its chordae tendineae* were not as clear cut The latter structures were tremendously thickened and were involved disproportionately to the two mitral leaflets themselves so that one wondered if actually this was an instance of rheumatic involvement There was no perivascular scarring or any evidence of an Aschoff body nor was there any endocardial lesion in the left auricle It was suggested that these changes might be those resulting from disseminated lupus erythematosus There were in the myocardium groups of leukocytes about some of the blood vessels but this was a very acute change and the etiology was undetermined

Summary This 51 year old electrician had been told he had a leaky heart at age 7 years One year before admission he developed dyspnea orthopnea and substernal pain Physical examination revealed signs of aortic insufficiency and possible mitral stenosis auricular fibrillation dilatation of the aorta congestive heart failure and possible pulmonary infarction The blood serologic test for syphilis was positive The evidences of heart failure were steadily progressive Analysis of the findings led to the conclusion that the patient had heart disease of either syphilitic or rheumatic etiology It was pointed out that all of the findings might be more satisfactorily accounted for if the patient had both syphilis of the aortic valve and rheumatic disease of the mitral valve Autopsy disclosed syphilis of the aorta and aortic valve and changes in the mitral leaflets and chordae tendineae without any rheumatic endocardial changes in the left auricle The mitral valve lesions were not typical of rheumatic endocarditis and the possibility of disseminated lupus erythematosus was suggested This then was an unusual case of AORTIC INSUFFICIENCY DUE TO SYPHILIS and mitral stenosis due to a different etiologic factor possibly an unusual type of rheumatic endocarditis possibly lupus erythematosus

II

(#544111 Admitted July 12 1950 Died July 20 1950)

THIS 37 year old white housewife was admitted because of heart trouble As a child she was never strong and did not engage in activities as much as did other children She did no housework because it tired her too quickly She remembered a prolonged febrile illness in childhood which was not relieved by tonsillectomy Following a second tonsillectomy however her fever subsided There was no other history suggestive of rheumatic fever

In 1948 she was told that something was wrong with her heart valves One year before admission she developed shortness of breath on exertion Orthopnea was also noted and she complained of generalized weakness She was digitalized but her dyspnea progressed in severity and she began to have intermittent edema of the ankles Nine weeks before admission her edema became more prominent She ate poorly and lost weight Four weeks before admission she began to have frequent attacks of vomiting Her condition grew progressively worse and for two weeks she was given intravenous feedings For several days she had complained of pain in the lower part of the back

PHYSICAL EXAMINATION on admission T 98 P 94 R 28 B P 125/40

The patient looked critically ill She was lying almost flat without apparent increase in her discomfort No skeletal abnormalities were made out The eyes were normal There was marked venous distention in the neck Vigorous pulsations were noted in the supraclavicular regions There was some prominence of the left chest anteriorly The lungs were clear to percussion and auscultation The heart was very active There was a diastolic thrill over the apex There was enlargement of the heart with the maximal impulse and the left border of dullness in the midaxillary line Dullness extended 4 cm to the right in the 4th interspace The rhythm was regular The second pulmonic sound was accentuated At the apex there were a presystolic crescendo murmur and a long blowing systolic murmur In the aortic region there was a loud diastolic murmur and a harsh systolic murmur transmitted into the vessels of the neck The liver edge was palpable at the iliac crest There was pitting edema over the lower portion of the legs The peripheral pulses were full and quick in character

COURSE IN THE HOSPITAL The patient did not improve At times a few fine rales were heard at the lung bases She was digitalized but the size of the liver did not change On July 20 it was noticed that her pulse was irregular that she was disoriented and that the edema had increased She died on the following day

LABORATORY DATA Hemoglobin 12 8 gm hematocrit 40 2 icteric index 20 sedimentation rate normal leukocyte count, 9 000 with 69% polymorphonuclear cells Urine specific gravity 1 023 trace of albumin, rare white cell on microscopic examination Blood nonprotein nitrogen 62 mg % on July 13 rising to 87 mg % on July 15 Chloride 84 3 mEq /L on July 13 and 76 2 mEq /L on July 19 Cholesterol 102 mg % Venous pressure 240 mm of water Circulation time 60 seconds (Decholin) Blood serologic test for syphilis negative Electrocardiogram P waves variable in size and shape QRS complexes showed normal axis duration and amplitude T wave were slightly depressed Interpretation was a shifting auricular pacemaker with digitalis effect on the T waves

DISCUSSION The basic disorder which led to the death of this patient seems to have been cardiac insufficiency There was a very high venous pressure marked slowing of the circulation time, massive hepatomegaly and peripheral edema There are two outstanding problems for discussion (1) the cause of the heart disease and (2) the reason for the onset and rapid progression of the heart failure

The clinical signs point to the presence of aortic insufficiency and this seems to offer the best feature for orienting the discussion of the cause of the heart disease

One of the most striking facts about this patient s illness was the steadily progressive downhill course with death occurring about one year after the onset of the first symptoms of cardiac failure As we have seen before such a relentless course usually indicates that the aortic insufficiency is due to syphilis However in this case there was neither historical nor serological evidence of syphilis

In considering the possibility of a rheumatic etiology we again encounter the familiar difficulty in determining whether the mitral valve was involved Only when the aortic insufficiency is slight and the signs of mitral stenosis predominate can one confidently make a diagnosis of both of these lesions In this case the aortic insufficiency was severe and the murmurs which might have been indicative of mitral stenosis constituted untrustworthy evidence The lack of a history of rheumatic fever or of other rheumatic manifestations is important but indecisive negative evidence We have learned in these conferences that too great importance may be attached to the presence or absence of a history of rheumatic manifestations Positive evidence must be critically appraised to avoid mistaking other forms of arthritis for acute rheumatic fever On the other hand it is well known that in some geographic areas including Baltimore a relatively high percentage of those who have chronic rheumatic heart disease give no

history of acute rheumatic fever or other recognizable evidences of preceding rheumatic disease More significant evidence pointing away from rheumatic heart disease was the rapid and steady progression of the heart failure rarely encountered in cases of rheumatic aortic insufficiency unless there is a complicating acute myocarditis or pericarditis

Although there were none of the classic evidences of subacute bacterial endocarditis this disease required serious consideration It may in some cases run a chronic indolent course and the presenting symptoms may be only those of a chronic valvular disease with superimposed heart failure Usually however there is at least a low grade fever and a mild anemia Neither was apparent in this case The renal insufficiency would be compatible with a diagnosis of bacterial endocarditis particularly since there was no hypertension However the severe grade of heart failure could alone account for the renal insufficiency There is no other sound reason for considering bacterial endocarditis as the cause of the aortic insufficiency

Since evidence in favor of the commoner causes of aortic insufficiency appears to be lacking in the present instance one must give particular attention to the rarer causes Relative aortic insufficiency occurs when there is enough dilatation of the aortic ring to prevent complete approximation of the cusps The degree of insufficiency is usually slight and the wide pulse pressure and other peripheral signs of aortic insufficiency are lacking However in some cases the incompetence of the valves may be great and there may be all of the classic peripheral phenomena This is true in some cases of dissecting aneurysm or in other conditions leading to great dilatation of the aorta such as syphilis and arteriosclerosis Occasionally considerable dilatation of the ring is seen in congenital defects In this case however there was no evidence in the clinical record of unusual widening of the aorta

The distinction between congenital defects and acquired heart disease often presents a problem which is complicated by the fact that the two may be associated in the same patient It is rather intriguing to consider one such defect as the cause of this patient s illness This defect consists in an opening at the base of the right aortic sinus of Valsalva leading into a finger or thimble like process which projects into the conus of the right ventricle and represents an aneurysm of its wall and that of the aortic sinus This aneurysm may rupture into the right ventricle and the clinical manifestations may simulate those

of aortic insufficiency of a severe degree This type of lesion might explain both the patient s life long incapacity for exertion and the rapidly progressive heart failure

CONCLUSIONS The absence of evidence of syphilis, rheumatic disease and bacterial endocarditis the history of incapacity for exertion beginning in childhood and the rapidly progressive heart failure during the last year of life lead to the conclusion that this patient had a congenital cardiac lesion which became complicated by some additional factor during that last year The rupture of a congenital aneurysmal type lesion such as has just been described appears to offer the best explanation of all the findings

ANATOMICAL DIAGNOSIS (Autopsy No 22512) Cystic medial degeneration of aorta Healed dissecting aneurysm of ascending aorta Dilatation of aortic ring aortic insufficiency Patent ductus arteriosus Dilated and hypertrophied heart *Fine myocardial scarring Chronic passive congestion* with marked central necrosis and fatty infiltration of liver Jaundice Hyperplasia of bone marrow Extramedullary hemopoiesis in spleen Hemangioma spleen Multiple fresh pulmonary infarcts and multiple pulmonary artery thrombi

The ascending aorta immediately above the valve had an annular dissecting aneurysm about 5 cm long which stopped abruptly at the level of the commissures and the sinuses of Valsalva There was a narrow free ridge at the lower border of the aneurysm which partially overlay the sinuses Section showed that the dissection occurred in the media and was associated with typical cystic medial degeneration There was a greatly dilated aortic ring which clearly resulted in aortic insufficiency There was extreme dilatation and quite marked hypertrophy of the left ventricle There was no intrinsic valvular disease The cause of the heart disease and the failure appeared quite straightforward except for the fact that there was a patency of the ductus arteriosus which was 2 to 3 cm wide It seemed possible that an appreciable shunt may have occurred through this ductus and the cardiac output may have been somewhat elevated by this condition as the ductus itself and its aortic ostium were very dilated

SUMMARY This 37 year old housewife had limited her activity since childhood At age 35 years she was found to have a leaky heart One year before death signs of cardiac insufficiency first appeared and progressed steadily In the cardiac examination signs of aortic insufficiency predominated Analysis of the findings led to a diagnosis of a congenital defect probably aneurysm of the right sinus of Valsalva with rupture into the right ventricle Autopsy revealed a HEALED DISSECTING ANEURYSM due to cystic degeneration of the aorta and relative incompetence of the aortic valve There was also a patent ductus arteriosus Thus two congenital anomalies had served to increase the mechanical load on the heart by producing both a relative aortic insufficiency and a shunt between the aorta and pulmonary conus This type of congenital malformation of the

aorta occurring frequently in association with ectopia lentis and leading to aneurysmal dilatation is one of the important conditions in which relative aortic insufficiency may be of marked degree The ectopia lentis may be slight and detectable only by slit lamp examination Slit lamp examination was not made in this case because the correct diagnosis was not considered during life

III

(#397135 Admitted December 16 1946 Died January 14 1947)

THIS 63 year old Negro waiter entered the hospital with manifestations of severe cardiac failure and fever of undetermined origin Between 1903 and 1908 he had gonorrhea on several occasions and at the age of 15 he had a penile lesion for which he received only local treatments

Syphilis was diagnosed in 1929 and he received a total of 18 injections intravenously The Wassermann reaction became negative He remained well until July 1946 when he suddenly developed severe dyspnea and a sense of fullness in the epigastrium which persisted for two days In August he had an attack of paroxysmal dyspnea after which he had persistent dyspnea on exertion and orthopnea with some edema of the ankles At this time the serologic test for syphilis was found to be positive Physical examination revealed cardiac manifestations which were interpreted as being due to aortic insufficiency on the basis of cardiovascular syphilis Beginning September 13 he was treated with a total of three million units of penicillin over a period of nine days He had a low grade fever which gradually abated during the treatment The heart was enlarged particularly to the left There was a systolic thrill both at the apex and at the base A loud blowing systolic murmur was heard over the whole precordium and a diastolic murmur was present which was loudest in the tricuspid area but was also audible over the aortic and pulmonic regions The pulse was Corrigan in type The blood pressure was 132/42 The liver edge was palpable 2 fingerbreadths below the costal margin Hemoglobin was 10 8 gm icterus index 6 sedimentation rate 25 mm corrected The urine was normal

The patient continued to have rather severe nocturnal dyspnea and edema of the ankles developed No change was noted in the character of the murmurs The liver remained swollen and tender On October 11 he complained of pain in his left side of one week s duration On December 16 impairment of the percussion note with bronchovesicular breath sounds and numerous medium rales were noted over the area of the right middle lobe

PHYSICAL EXAMINATION on admission T 102 P 110 R 28 B P 130/40

The patient was thin markedly dyspneic and mildly cyanotic There was no edema The pupils reacted normally Fundi showed tortuosity of the vessels and some arteriovenous nicking but no hemorrhages or exudates There were numerous crackling rales at both lung bases and in both

axillae The heart was enlarged to the left measuring 13 cm in the 6th interspace The impulse was diffusely visible with no thrill or shock detectable Systolic and diastolic murmurs were audible over the entire precordium The pulse was collapsing in type The peripheral vessels were thickened and tortuous The liver edge was percussed 2 fingerbreadths below the costal margin There was clubbing of the fingers and toes

COURSE IN THE HOSPITAL The patient ran a daily elevation of temperature ranging from 102° to 103° with a rapid pulse rate It was thought that he might have bronchopneumonia and penicillin treatment was instituted One blood culture was reported initially to show gram positive cocci in chains (later identified as a *Staphylococcus albus*) The signs of heart failure diminished but the fever persisted A few days before death the patient developed auricular flutter with two to one block and a ventricular rate of 154 He became unresponsive cold clammy and more cyanotic On January 13 the patient s pulse rate suddenly dropped to 60 and he developed profound vascular collapse

LABORATORY DATA Hematocrit 41 % Leukocyte count 8 320 with juvenile neutrophils 9/ segmented neutrophils 71/ and monocytes 20/ Nonprotein nitrogen on December 26 55 mg % and on January 13 105 mg / Venous pressure 55 mm of saline Circulation time 18 sec Vital capacity 1100 cc X ray examination of the chest showed a mild infiltration at the right base The heart was enlarged particularly to the left

DISCUSSION The problem here is to determine the cause of the valvular heart disease which resulted in cardiac insufficiency and to account for the final illness which was associated with a persistent elevation in temperature in the face of improvement in the degree of heart failure

From the descriptions there can be no doubt that this patient had aortic insufficiency and differential diagnosis will be discussed with this as the orienting feature Of the various rheumatic valvular lesions aortic insufficiency is likely to give symptoms earlier than the others Since this lesion was first discovered when the patient was quite elderly and he previously had had no cardiac symptoms the chances are against a rheumatic etiology As a rule valvular lesions in rheumatic fever are multiple It is very difficult to go further than to say that this patient had aortic insufficiency In the presence of a pronounced degree of incompetence of this valve one can place no dependence upon the auscultatory signs of mitral disease Perhaps the strongest evidence for a rheumatic background was the rather harsh systolic murmur at the base and the presence on occasion of a systolic thrill in this area suggestive of some stenosis of the aortic valve

It seems quite clear from the record that this patient did have syphilis As has been pointed out there were suggestive signs of

aortic stenosis which would be a definite point against syphilis of the aortic valve However, there are other considerations which must be weighed in this regard and these will be discussed at a later point

There is little need to discuss so called calcific aortic stenosis The physical signs in this condition are predominantly those of stenosis although one may hear the typical diastolic murmur of aortic insufficiency

Occasionally one sees aortic insufficiency due to bacterial endo carditis in which the infection began on perfectly healthy valves In most instances however the valve has been the seat of damage usually the result of rheumatic fever a congenital deformity or syph ilis There are certain other features of this case which may be of importance This patient apparently had a subacute infection of some variety at the time of his first hospital admission when he was treated for syphilis with penicillin During the course of treatment the tem perature returned to normal On the final admission he was obviously in heart failure when first seen but even though this improved the fever failed to subside

Bacterial endocarditis may be easily diagnosed when the clinical features are fully developed However it is not always appreciated that chronic forms may occur in which mild and atypical symptoms are present over a long period of time This is particularly true now when penicillin is given for almost any elevation in temperature If the patient happens to have an unrecognized bacterial endocarditis and the treatment with penicillin is inadequate for its eradication then a bizarre clinical picture may result One may see no charac teristic embolic manifestations there may be no splenomegaly little or no anemia and the fever may be slight irregular and variable in its course In the present case one has little to go on There was during the first admission a low grade fever which subsided during treatment with penicillin There was some drop in hemoglobin but unless one interprets the episode of pain in the abdomen as such there were no recorded embolic phenomena The urine contained no red cells and there was no splenomegaly There was clubbing of the fingers and on one occasion an organism was grown from the blood stream although this may have been a contaminant

If one reviews the cardiac findings it is to be noted that there was a systolic thrill over the base of the heart in the early examinations but not at the final admission One could postulate that at first there was a cluster of vegetations and that the treatment with penicillin caused sufficient healing so that by the time of the second admission

the circulatory findings suggesting aortic stenosis had disappeared It is noteworthy that there was some nitrogen retention in spite of an adequate urinary volume, and in the absence of any elevation of blood pressure Renal insufficiency is not an infrequent finding during the course of bacterial endocarditis and the renal lesion may not be accompanied by an elevation in blood pressure A shocklike picture developed just before death Auricular flutter with two to one block was noted This suggests that some sudden change took place in the cardiovascular system and it is possible that the patient had a coronary embolus arising from bacterial vegetations or possibly a pulmonary embolus on the basis of a mural thrombus or from a peripheral source

One must consider that the final febrile illness may have had no direct relationship to the patient s cardiac disease However no evidence for any other type of infection was found In addition there was nothing in the examination which would lead one to believe that causes other than an infection may have been present as a basis for the febrile response

One can tie together all of the findings in the most logical sequence if it is assumed that this man had aortic insufficiency with bacterial endocarditis The course of events suggests that the bacterial lesions were implanted on a valve previously damaged by syphilis This is an infrequent occurrence but in the present case it seems to offer the best explanation of the findings

ANATOMICAL DIAGNOSIS (Autopsy No 20367) *Healing subacute* bacterial endocarditis of aortic valve with perforation of cusp Healed mycotic aneurysm sinus of Valsalva Aortic insufficiency Cardiac hypertrophy and dilatation Chronic passive congestion of viscera Infarcts of kidneys Sclerosis of coronary arteries Lobular pneumonia Pulmonary emphysema

The heart was greatly enlarged with dilatation and hypertrophy of the left ventricle The aortic cusps were greatly altered by rough calcareous deposits and there was a definite healing bacterial endocarditis which had frayed the valve margins produced a perforation of one cusp and obviously had created a marked insufficiency There was a depressed area in a sinus of Valsalva which suggested a healed early mycotic aneurysm There was no suggestion of syphilis rheumatic fever or arteriosclerosis of the aortic valve

SUMMARY This elderly Negro man had a history of treated syphilis Seven months before death he developed dyspnea and was found to have aortic insufficiency A diagnosis of syphilis was made and he received a course of penicillin Evidence of cardiac insufficiency persisted with development of pain in the left side fever and signs of pneumonia over

the right middle lobe Examination revealed fever aortic insufficiency hepatomegaly and clubbing of the fingers The signs of cardiac insufficiency improved but the fever persisted Auricular flutter developed and the patient died in collapse a few days later A low grade fever which abated during penicillin treatment for syphilis and a mild unexplained anemia were the initial clues to the diagnosis of BACTERIAL ENDOCARDITIS which had developed on a normal heart valve and had evidently healed incompletely during the brief course of penicillin given for treatment of the syphilis

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Chapter 2

HEART FAILURE

THE PHYSICIAN is often called upon to see patients in whom the clinical picture is dominated by the manifestations of myo cardial insufficiency In order to carry out proper treatment he must determine why the heart is incapable of performing the work required of it and *he must seek a reasonable explanation of the sequence of* events which led up to this state of incompetency

The diagnosis of cardiac failure is never based solely upon the examination of the heart In fact the heart may be greatly hyper trophied its rhythm may be totally irregular and there may be loud murmurs and a grossly abnormal electrocardiogram without the existence of any evidence of failure On the other hand there may be clear cut evidences of failure when the examination of the heart dis closes only slight and questionable abnormalities The diagnosis of failure is based upon the more remote physiological and anatomical evidences of inadequate cardiac function In the less severe types of failure these evidences make their appearance only during periods of physical or emotional stress In such cases the diagnosis may depend *upon the patient s history rather than upon the physical findings* As the failure becomes more severe the physical signs may be detected at first during exercise and later while the patient is at rest

CONGESTIVE HEART FAILURE

This chapter deals primarily with the type of heart failure which is called backward or congestive failure The congestion may involve either the lesser (pulmonary) or the greater (systemic) circulation or it may involve both of these circuits The term frequently employed to designate passive congestion of the pulmonary circulation is left ventricular failure while passive congestion of the systemic circula tion is designated right ventricular failure In the majority of cases

the congestion affects both circuits although it may predominate in one or the other Primary right ventricular failure may be due to lesions in the right side of the heart, the lungs or the mediastinum which interfere with the filling or emptying of the chambers of the right side of the heart Secondary right ventricular failure may be due to lesions in the left side of the heart which obstruct the flow of blood through the lungs The principal evidences of right ventricular failure are elevated venous pressure, distention of the systemic veins, enlargement of the liver and accumulation of edema fluid in tissue spaces and serous cavities Right ventricular failure must be differentiated from conditions which cause localized or generalized obstruction of the veins or lymphatics conditions which cause enlargement of the liver and conditions which lead to the production of edema Left ventricular failure may be due to lesions in the left side of the heart mediastinum or peripheral arteries which interfere with the filling or emptying of the chambers of the left side of the heart The principal evidences of this type of failure are dyspnea cough distention of the pulmonary vessels reduced vital capacity of the lungs signs of transudation of fluid into the alveoli and small bronchi Left ventricular failure must be differentiated from those diseases of the lungs and pleura which have similar manifestations and it must also be differentiated from conditions which lead to a reduction in the oxygen carrying capacity of the blood

Eichna and his co workers have presented observations which indicate that systemic and pulmonic vascular congestion is not a specific hemodynamic manifestation but that such congestion may arise on a non myocardial basis producing a picture however which is clinically indistinguishable from that seen in congestive heart failure This type of circulatory congestion, which they term as non cardiac in origin is seen in situations characterized by mechanical obstruction to blood flow within the heart such as mitral stenosis of the pinch cock type situations characterized bv excessive accumulation of water and salt in patients without heart disease, such as acute glomerulonephritis and situations usually labelled as high output failure including beriberi and severe anemia in patients without previous cardiac disease

The causes of heart failure may be grouped in a varietv of ways An etiological classification is the one most frequently offered Although it is desirable always to strive for an etiologic diagnosis it may be more practical and ultimately just as fruitful to begin one s consideration of the problem in a somewhat simpler frame of refer

ence In 1938 Dr Louis Hamman proposed a classification which has no intrinsic merit other than its simplicity and the fact that experience both in the clinic and in the preparation of clinical pathological con ferences has proved it to be a very convenient and productive approach to the differential diagnosis of cardiac failure This classification has been modified as shown in Table 1

In attempting to assign a case to its proper position in the cate gories enumerated in the table it must be realized that a schematic arrangement of this type does not always permit clear cut distinc tions A combination of two or even more factors may come into play in a single case For example in many cases of valvular disease the immediate cause of the failure may be active disease of the myo cardium From another point of view both systemic hypertension and hypertension in the pulmonary circulation may be the result rather than the cause of cardiac failure In studying the proposed classifica tion one practical point stands out namely that the heart fails in most instances because it has been working for a long period of time at a mechanical disadvantage A mechanical factor is either the prin cipal cause or an important contributory cause of heart failure in the majority of cases It is therefore eminently practical to assume in all cases that a mechanical factor has contributed to the failure and to abandon this view only when a careful consideration of all the evidence compels one to seek another explanation If one refuses to attribute the failure to primary disease of the myocardium until after he has eliminated in order the possible mechanical causes he will be less likely to neglect the important but frequently overlooked in stances of failure due to disease of the pericardium to hypertension of the pulmonary circulation and to some of the rarer cardiac conditions

The various causes of heart failure will now be considered in the order of their classification

FAILURE ASSOCIATED WITH VALVULAR DEFECTS

Physiologically significant disease of the heart valves almost invari ably results in the production of a cardiac murmur High grade mitral stenosis is occasionally found in persons who come to autopsy without any murmur having been detected during life In some instances this may be accounted for by lack of thoroughness on the part of the examiner The murmur of mitral stenosis may be con fined to a small area and it may be heard only when the patient is in the left lateral position A brief period of exercise may also bring

Table 1 Causes of Congestive Heart Failure and Non-cardiac Circulatory Congestion (Modified after Hamman)

I Valvular heart disease
- A Rheumatic
- B Syphilitic
- C Congenital
- D Calcareous or arteriosclerotic
- E Acute or chronic due to infection
- F Rarer causes such as systemic lupus erythematosus

II Systemic hypertension
- A Due to vascular disease
  - 1 Coarction of the aorta
  - 2 Arterial disease
    - a periarteritis nodosa
    - b thromboangiitis obliterans
    - c systemic lupus erythematosus
  - 3 Renal artery embolism or thrombosis
  - 4 Renal arteriosclerosis
  - 5 Congenital defects in the renal circulation
  - 6 Dissecting aneurysm involving the renal vessels
  - 7 Tumor or extrarenal mass (aneurysm) with compression of renal arteries
- B Parenchymal renal involvement
  - 1 Acute or chronic glomerulonephritis
  - 2 Chronic pyelonephritis
  - 3 Congenital polycystic kidneys
  - 4 Congenital renal defects
  - 5 Tumors
- C Endocrine factors
  - 1 Pheochromocytoma
  - 2 Cushing s syndrome
  - 3 Adrenocortical adenoma or carcinoma
- D Essential hypertension

III Hypertension in the lesser circulation
- A Secondary (e g mitral stenosis auricular myxoma large auricular thrombus)
- B Primary
  - 1 Obstruction to arterial blood flow
    - a arteriosclerosis
    - b recurrent pulmonary emboli or thrombosis
  - 2 Chronic pulmonary disease
    - a emphysema
    - b diffuse fibrosis

IV Failure associated with pericarditis
- A Pericardial effusion or hemorrhage with tamponade
- B Chronic constrictive pericarditis
- C Adhesive mediastinopericarditis

V Congenital heart disease

VI Failure due to disease of the myocardium
- A Infections

- B Intoxication or sensitivity to drugs
- C Disease due to nutritional defects or changes in the circulating blood
- D Changes secondary to inadequacy of the blood supply to the heart muscle
- E Myocardial involvement in the course of certain systemic diseases (e g amyloidosis hemochromatosis)

VII Failure associated with miscellaneous rare conditions
- A Tumors of the heart
- B Deformities of the thorax
- C Trauma
- D Constrictive endocarditis
- E Arteriovenous aneurysms

out a murmur which is otherwise inaudible The diastolic murmur of aortic insufficiency may also escape detection in some cases In the early phase of its development this murmur may be heard only in a small area to the left of the sternum It has a soft far away quality which may elude all ears except those which have been made receptive by experience Such murmurs are more readily detected with the diaphragm than with the bell stethoscope and on occasions still more readily with the naked ear

Errors of omission such as those mentioned above are much less common in the field of cardiac auscultation than are errors of interpretation Murmurs are far more frequent than valvular lesions and it is difficult in many cases of heart failure to decide whether a murmur is actually attributable to anatomical changes in the valves The murmurs which occur in diastole are usually a reliable index of valvular disease But even here one must exclude the diastolic murmurs produced by congenital defects and by relative insufficiency of the aortic and pulmonic valves Systolic murmurs may be heard in people who are in perfect health as well as in those who have a variety of pathological conditions not affecting the structure of the heart valves The murmurs heard in healthy individuals frequently have a tendency to diminish in intensity or even disappear in certain phases of respiration or when the posture of the body is changed The systolic murmurs associated with anemia fever or hyperthyroidism are heard usually at the apex of the heart or in the pulmonic area They may be quite loud and rough and fail to show any change with respiration or with alterations in posture In almost all cases in which the heart is dilated a systolic murmur may be heard in the apical region This murmur may have the rasping quality of an organic mitral murmur and may be transmitted into the axilla and back In children almost any infection is accompanied by an apical systolic murmur In patients over the age of 50 years a systolic murmur is

quite frequently heard in the aortic area This murmur may be due to calcific changes in the aortic cusps but in other instances it appears to be due to dilatation or roughening of the aortic wall or to narrowing of the orifices of the great vessels emerging from the base of the aorta In occasional cases of dilatation of the heart there may appear at the base of the xiphoid a loud, rather high pitched systolic murmur which disappears as the dilatation diminishes and reappears as the dilatation returns This murmur in most instances cannot be explained by organic valve disease and is presumably due to relative insufficiency of the tricuspid valve

The various murmurs just mentioned are only examples of the types of murmurs which may be heard in the absence of organic disease of the valves It seems unnecessary here to review the characteristics of the murmurs produced by valvular defects Detailed descriptions may be found in any textbook It should be emphasized, however that the interpretation of murmurs particularly those which occur during systole can be based only in part upon their location and auditory characteristics Many other factors must be considered such as accompanying thrills alterations in the quality and intensity of the heart sounds the quality of the pulse the fullness and pulsation of the veins and liver the size and configuration of the heart, and the relative preponderance of the ventricles Very important and often decisive is the presence of some associated disease which may account for the murmurs in the absence of valvular defects An apical systolic murmur so frequently heard in all types of cardiac failure should be interpreted as evidence of structural valvular disease only when the associated circumstances strongly point to such a conclusion This cautious attitude should not lead one to disregard the relatively inconspicuous murmurs which may be encountered in the early phases of bacterial endocarditis

Once it has been decided that the cardiac failure is associated with a valvular defect one may proceed to the consideration of etiology The differential diagnosis of insufficiency of the aortic valve has been discussed in Chapter I The same general principles apply to the differential diagnosis of lesions of the other heart valves The mitral valve is far more frequently affected than the valves of the right side of the heart and in the vast majority of cases the mitral defect is due to rheumatic disease Active bacterial endocarditis healed bacterial endocarditis and calcific disease and congenital malformations of the valve must also be considered When congenital or acquired mitral stenosis is associated with an auricular septal defect it may lead to

the production of the so called *Lutembacher syndrome* in which the signs of mitral stenosis are accompanied in most instances by great dilatation of the pulmonary artery and a harsh rasping systolic murmur and thrill at the base of the heart This spectacular syndrome is for some unexplained reason almost never complicated by the development of bacterial endocarditis The accurate diagnosis of mitral stenosis offers a particular challenge at the present time owing to the increasing effectiveness of the surgical treatment of this condition The relief of cardiac failure which follows mitral valvulotomy even in the presence of active rheumatic myocarditis affords a striking example of the role of the mechanical factor in the production of myocardial insufficiency

FAILURE ASSOCIATED WITH ARTERIAL HYPERTENSION

The heart has a remarkable ability to function efficiently over a period of many years in spite of the increased load imposed by considerable degrees of arterial hypertension In some cases it is difficult to determine just what factor has precipitated failure Frequently the first departure from normal compensation occurs in the form of acute pulmonary edema following some unusual exertion or excitement The patient may recover rapidly from such an episode and under appropriate treatment may have no further evidences of failure for a period of many months On the other hand the heart may never regain a fully compensated state the signs of pulmonary congestion may persist and these may be followed by the gradual development of peripheral congestion *Occlusive disease of the coronary arteries* by reducing the blood flow to the myocardium may render the hypertensive heart incapable of meeting peak loads and finally may so reduce its reserve that it can no longer contend with the elevated pressure even during normal activities Such patients may have angina pectoris as well as evidences of failure In some of these cases the final episode of failure is due to myocardial infarction Under these circumstances the true pathogenesis of the condition may be obscured by the fact that the blood pressure falls to normal at the time of the infarction On the other hand it is well to remember that in certain cases of heart failure the blood pressure rises during the period of decompensation and returns to normal as the efficiency of the heart improves

In all cases of failure associated with hypertension it is important to exclude the possibility of coarctation of the aorta This type of failure is now amenable to radical cure by surgery For the same

reason pheochromocytoma should be excluded in all cases of hypertensive heart failure

A peculiar type of failure associated with hypertension is that seen in the so called *Bernheim syndrome* In this condition the greatly hypertrophied left ventricle so encroaches upon the cavity of the right ventricle that the flow of blood through the right side of the heart is partially obstructed and peripheral congestion occurs in the absence of any signs of pulmonary congestion This is the reverse of the type of failure usually encountered in cases of hypertension

FAILURE ASSOCIATED WITH HYPERTENSION IN THE PULMONARY CIRCULATION

In this category we include only those patients who have primary pulmonary hypertension Secondary pulmonary hypertension is due to congestion in the pulmonary veins caused usually by conditions which impede the flow of blood through the left side of the heart It is found most frequently in cases of mitral stenosis and in the various forms of left ventricular failure Primary pulmonary hypertension on the other hand is caused by disturbances within the lungs which obstruct the flow of blood through the pulmonary arteries Such obstruction may be due to disease of the walls of the pulmonary arteries or arterioles emphysema pulmonary fibrosis thrombosis of the pulmonary artery or its branches or large emboli in the branches of the pulmonary artery which do not immediately result in death Some of these obstructive lesions, for example emphysema and fibrosis may be detected in roentgenograms of the chest Other lesions such as emboli may be suspected on the basis of the x ray findings However in a number of cases the pulmonary hypertension is considered to be primary in type only because the causes of secondary pulmonary hypertension have been sought and excluded

The diagnosis of pulmonary hypertension can be made with accuracy by catheterization of the pulmonary artery Without this specialized and frequently unavailable technique the diagnosis depends upon the detection of the consequences of increased pressure within the pulmonary artery and it is reinforced by the discovery of any of those conditions which are known to obstruct the pulmonary arterial blood flow The consequences of pulmonary hypertension are dilatation of the pulmonary artery and its branches dilatation and hypertrophy of the chambers of the right side of the heart and an increase in the intensity of the second heart sound in the pulmonic area Hypertrophy of the right ventricle is evidenced in some cases by a conspicuous forceful heave of the lower portion of the sternum Evi

dence of right ventricular enlargement may also be found in roentgenographic studies and in electrocardiographic tracings A secondary polycythemia may be present

Sustained hypertension in the pulmonary circulation eventually leads to failure of the right ventricle with resulting engorgement of the veins enlargement of the liver and edema Cyanosis when already present as a result of the primary intrapulmonary disease may *become very conspicuous when the right ventricle fails*

FAILURE ASSOCIATED WITH PERICARDITIS

This type of failure is much less common than those enumerated above and probably for this reason it is likely to receive less attention in differential diagnosis However no type of failure is more important to recognize since the therapeutic potentialities are great and the consequences of neglect may be disastrous Pericarditis may lead to cardiac failure in one of three ways (1) large pericardial effusions may interfere with the diastolic expansion of the heart and thus reduce its efficiency as a pump (2) thickening scarring and contraction of the pericardium so called constrictive pericarditis may likewise interfere with the diastolic filling of the heart (3) adhesions formed between the heart and the surrounding structures of the thoracic wall mediastinum and diaphragm may interfere with systolic emptying of the heart Of these three conditions the third is probably of least significance It is rarely the sole cause of cardiac failure although it may be a contributory cause when combined with other factors Pericardial effusion should be kept in mind in any case in which the area of cardiac dullness is large and precordial pulsations are difficult to find A rapid increase in the size of the area of dullness should always arouse suspicion The contour of the cardiac shadow in roentgenograms particularly when pictures are taken in various postures and the reduced amplitude of the cardiac contrac*tions noted by fluoroscopy are very helpful aids to diagnosis* The electrocardiogram may reveal the S T segment changes characteristic of an acute pericarditis Constrictive pericarditis should be suspected in cases of chronic right heart failure in which ascites and hepatomegaly are conspicuous manifestations Here again the fluoroscopic *examination yields valuable evidence for diagnosis*

FAILURE ASSOCIATED WITH CONGENITAL DEFECTS

The facts which emerge from a detailed history and the unusual quality temporal relations and location of murmurs most often lead

one to suspect the presence of congenital cardiovascular anomalies The recent development of appropriate surgical methods to deal with some of the various defects makes precision in diagnosis far more important than it was several years ago The exact localization of these lesions has become almost a specialty in itself Taussig s practical treatise entitled *Congenital Malformations of the Heart*, provides a clear and comprehensive view of the clinical aspects of this complicated subject In reading this volume one is impressed by the importance of careful history taking and meticulous study of the physical abnormalities these combined with detailed roentgenographic studies and a knowledge of the possibilities which exist will serve to unravel many of the most complex diagnostic problems The ballistocardiogram and electrocardiogram are sometimes helpful Special techniques such as cardiac catheterization and angiocardiography give decisive information in some cases but it is impressive how infrequently such studies are required to achieve accurate diagnosis of the more common and important types of anomalies

In adults the congenital anomalies most frequently encountered are septal defects patent ductus arteriosus and coarctation of the aorta The last two of these are the most important to differentiate because they are less frequently associated with other serious anomalies and are peculiarly suitable for surgical treatment Coarctation of the aorta may be easily recognized if its presence is suspected In any case of hypertension it is truly unforgivable not to palpate the pulses in the arteries of the lower extremities and it is better practice to record the blood pressure in the legs at the time of the initial examination If these simple precautions are observed significant degrees of coarctation will not be overlooked Patent ductus arteriosus is not always so easily detected In some cases particularly during adolescence the characteristic murmur and thrill in the left subclavicular region may be totally absent

FAILURE DUE TO DISEASE OF THE MYOCARDIUM

If one can satisfactorily exclude the five categories described above then it may be assumed that the cause of the cardiac failure is disease of the myocardium (A few rare exceptions will be mentioned in the succeeding section) The diagnosis need not always be one of exclusion for the electrocardiogram may give positive evidence of myocardial damage Except in cases of myocardial infarction the clinical evidences of myocardial disease are too variable to provide an adequate basis for positive diagnosis Signs frequently encountered are

dilatation of the heart, feeble precordial impulse weak heart sounds gallop rhythm systolic murmur at the apex small pulse pressure Myocarditis may lead to great enlargement of the heart In the differential diagnosis of such cases particular consideration must be given to the possibility of pericardial disease The heart may reach enormous proportions in consequence of adhesive pericardio mediastinitis But of greater importance from the point of view of immediate therapy is the detection of cases in which pericardial effusion simulates cardiac enlargement Even after a pericardial paracentesis has been performed doubt may still exist owing to the fact that the pericardial fluid may be grossly bloody and thus give rise to a suspicion that the needle had entered the heart The uncertainty may be resolved by injecting a small amount of dye through the paracentesis needle and examining a sample of blood to determine whether the dye has entered the blood stream or has been trapped in the pericardial cavity Further discussion of the differential diagnosis of the various types of myocardial disease will be found in the case reports

FAILURE ASSOCIATED WITH MISCELLANEOUS RARE CONDITIONS

It is not intended here to enumerate all of the rare conditions which may cause cardiac failure Emphasis will be placed chiefly upon those conditions which if recognized may be successfully treated

Tumors of the Heart Most tumors of the heart are secondary to tumors arising in other structures They reach the heart either by metastasis or by direct extension chiefly from the lungs or pleura Heart failure results either from involvement of the myocardium or from obstruction of the flow of blood through the heart Primary tumors of the heart are rare and the more common types are relatively non malignant Congenital rhabdomyomas are encountered usually in early childhood and are almost always associated with other congenital anomalies A primary heart tumor which is of particular diagnostic importance is the solitary pedunculated myxoma which arises from the interauricular septum usually from the left side of the septum near the foramen ovale As the tumor grows it encroaches upon the mitral orifice In some cases it dangles within the lip of the mitral ring like a large grape and leads to intermittent ball valve obstruction There may result transient periods of syncope or sudden episodes of dyspnea The most striking physical signs are those attributable to mitral stenosis and progressive congestive failure Although these tumors are uncommon they are encountered oc

casionally in most large clinics One of us has personally examined two such cases and the second was so like the first that the correct diagnosis was suspected several days before the patient died In a third case presented by one of us at a clinical pathological conference the correct diagnosis was made on the basis of the observations recorded in the clinical history The diagnosis can be accurately established during life by means of angiocardiography as in a case reported by Bahnson and Newman in which such a tumor was present in the right auricle and was removed at operation This procedure should certainly be employed in any case in which a myxoma of the heart is suspected *If the diagnosis can be established with reasonable accuracy* the excision of the tumor presents a challenge to the cardiac surgeon

DEFORMITIES OF THE THORAX In patients who have extreme degrees of kyphoscoliosis or other structural distortion of the thorax there may be mechanical interference with the function of the heart and lungs The failure which results *is* usually of the right ventricular type and it is perhaps more appropriately designated pulmonocardiac failure In some cases the mechanical factors may be at least partially corrected by surgical means

The following case history (M I B H No 41272) indicates how *heart failure may develop suddenly in an individual who has had a* deformity of the thorax for many years

Cor pulmonale with sudden heart failure occurred in a middle aged woman with long standing deformity of the thorax which had resulted in compression atelectasis and fibrosis of the right lung and compensatory emphysema of the left lung Marked temporary improvement followed a massive hemorrhage from the intestinal tract The final episode of heart failure was precipitated by a respiratory tract infection Throughout the period of observation there was a respiratory type of acidosis

A white housewife aged 49 years had an extreme degree of kyphoscoliosis dating back at least to early adolescence In spite of the skeletal deformity she had led an active life and had three healthy sons, the youngest aged 24 years She had had no cardiorespiratory symptoms until three days before entering the hospital in May 1949 At that time she had rather suddenly become dyspneic and her husband had noted for the first time that her color had a bluish tinge The dyspnea continued without remission It was not increased when she lay flat Two days before admission the ankles began to swell and the patient became nauseated When first examined she was extremely

dyspneic and cyanotic Pulse was 100 respiratory rate 32 blood pressure 130/92 There was marked distortion of the thorax due to curvature of the dorsal spine Scoliosis toward the right was so great that the right side of the chest was markedly contracted and failed to expand during inspiration Kyphosis was so great that the lower ribs rested on the iliac crests There were numerous rales over the lower two thirds of the lung fields The size of the heart could not be estimated because of the thoracic deformity The sounds were clearly audible rhythm was regular The second sound was split at the base of the heart and was louder in the pulmonic than in the aortic area No murmurs were heard The liver edge was felt 5 cm below the costal margin There was slight edema of the ankles X ray pictures of the chest showed marked engorgement of the pulmonary vessels The electrocardiogram showed a right axis deviation

With bed rest and oxygen the cyanosis and dyspnea rapidly diminished However whenever the patient was removed from the oxygen tent her symptoms returned Four days after admission she had a large gastrointestinal hemorrhage The hemoglobin fell from 17 1 gm to 7 6 gm the red blood count from 5 8 million to 2 7 million and the arterial pressure from 132/92 to 100/60 She continued to pass blood in the stools for six days and during this period received six blood transfusions Following this episode the patient s condition improved remarkably The cyanosis almost disappeared Dyspnea subsided The rales disappeared from the lungs and the venous pressure fell from 210 to 75 mm water She was discharged from the hospital 17 days after the hemorrhage in excellent condition In spite of the improvement there was no appreciable change in the blood chemical acidosis on admission CO_2 38 7 mEq /L chloride 90 3 mEq /L five days before discharge CO_2 37 2 mEq /L chloride 96 4 mEq /L

While at home on digitoxin and a low salt diet the patient was up and about and was quite comfortable She was readmitted to the hospital September 21 1949 five days after developing a respiratory tract infection with fever On entering the hospital her general appearance was about the same as at the time of the first hospital admission There were marked dyspnea and cyanosis distention of the neck veins rales throughout the lungs and a large tender liver

On this occasion the acidosis was more marked than at the first admission the serum CO_2 varied from 34 9 to 45 7 mEq /L and the chloride from 77 0 to 82 0 mEq /L The cyanosis failed to clear even when the patient was in an oxygen tent The rales diminished some

what but failed to clear up The respiratory rate was almost constantly rapid, varying from 24 to 40 per minute The patient became exhausted stuporous, and finally died of respiratory failure while the heart sounds were still strong

The important findings at autopsy were kyphoscoliosis atelectasis and interstitial fibrosis of the right lung and emphysema of the left lung The heart was enlarged weight 360 gm, and it presented the appearance of *cor pulmonale* with marked hypertrophy and dilatation of the right ventricle The left ventricle pericardium, heart valves and coronary arteries were normal in appearance There was marked passive congestion of the liver kidneys stomach and intestines The hemorrhage from the intestinal tract was evidently due to passive congestion no tumor or ulceration being found

TRAUMA Trauma may lead to heart failure in one or more of several ways rupture of a heart valve disturbance in cardiac rhythm, hemopericardium or contusion of the myocardium The external evidences of injury may be so slight as to escape attention Acute hemopericardium with cardiac tamponade may be mistaken for post-traumatic shock Fluoroscopic and electrokymographic examinations are of great assistance in establishing the correct diagnosis Prompt removal of the blood from the pericardium usually brings about a dramatic improvement in the circulation If blood continues to accumulate in the pericardium the heart should be explored surgically

CONSTRICTIVE ENDOCARDITIS Constrictive endocarditis is a very rare condition which presents a clinical picture similar to that seen in constrictive pericarditis

PERIPHERAL CIRCULATORY FAILURE IN PATIENTS WITH AND WITHOUT HEART DISEASE

In Table 2 are listed those conditions which result in circulatory insufficiency with hypotension The symptoms associated with peripheral circulatory insufficiency are the result of a serious decrease in cardiac output or a precipitous fall in arterial pressure as a consequence of arteriolar dilatation In the circumstances listed under the second category in the table the fall in cardiac output results from an inadequate venous return, but under other circumstances it may result from failure of the heart to pump sufficient blood, as occurs after an acute myocardial infarction, or from failure of proper ventricular filling, as in pericardial tamponade The various types of disease in which this clinical picture may develop will not be dis

Table 2 Circulatory Insufficiency with Hypotension and without Signs of Congestive Heart Failure (Modified after Stead)

1 Associated with reflex arteriolar and vein dilatation
  a Fainting attack
  b Syncope due to drugs (nitrites)

2 Failure of adequate venous return to the heart as a result of lowered blood volume
  a *Hemorrhage*
  b Extensive loss of plasma
  c Severe dehydration

3 Pericardial tamponade
  a Intrapericardial hemorrhage
  b Acute pericarditis with effusion

4 Medical shock associated with severe illness
  a Overwhelming infection
  b *Severe hepatic disease*
  c Central nervous system involvement
  d Severe hypoglycemia
  e Adrenal insufficiency

5 Obstruction of a major arterial pathway
  a Cerebral thrombosis or embolism
  b Pulmonary embolus
  c Coronary thrombosis

6 Failure of the heart muscle with low cardiac output
  a *Myocardial infarction*
  b Acute myocarditis

cussed in detail but the following abbreviated case report (JHH 261253) will serve as an example of this type of problem

Recurrent attacks of syncope over a period of 15 months in a 63 year old white woman with calcific aortic stenosis Following the third episode she developed the picture of hypotension requiring continuous infusion of norepinephrine Later there were clinical evidences of myocardial dis ease and the electrocardiogram showed changes of coronary insuffi ciency At autopsy in addition to the aortic valvular disease there were multiple small myocardial infarcts resulting from repeated coronary emboli the source of which could not be identified

During the 15 months preceding admission this 63 year old woman who had complained of dyspnea and mild ankle edema had two attacks of syncope preceded by epigastric discomfort and followed by no sequelae A similar attack developed the day of admission and on arrival at the hospital she was cold cyanotic and without audible heart sounds and the systolic blood pressure was 65 Following the institution of an infusion of norepinephrine the pressure rose to

100/70 The heart was not enlarged there was no evident venous distention but moist rales were heard at both lung bases In the aortic area transmitted into the vessels of the neck, was a harsh systolic murmur of moderate intensity

During the next ten days she had several similar episodes and the blood pressure had to be maintained by the continuous infusion of norepinephrine Her respirations became asthmatic in type, she remained cyanotic the heart sounds were poor in quality and there was a protodiastolic gallop rhythm

Her pressure became more and more difficult to maintain and a marked tachycardia developed On the eleventh hospital day her tension suddenly fell she became apneic and failed to respond to artificial respiration and respiratory or cardiac stimulants

On admission the electrocardiogram showed frequent premature ventricular contractions with diphasic T waves in V3 and V5 with S T segment changes suggestive of coronary insufficiency In subsequent records there was general flattening of the T waves and the S T segment in V3 was depressed In the chest x ray no cardiac enlargement was noted but there was widespread flocculent opacification extending from the hilar regions into both lung fields

It seemed reasonable to assume on the basis of the physical findings that there was a stenotic lesion of the aortic valve In such a situation attacks of syncope are not uncommon but it seemed necessary to search for some additional factor in view of the persistent hypotension following the third episode and the signs indicating myocardial involvement which subsequently developed She also had fever and some leukocytosis There was no evidence of an inadequate return of blood to the heart or a disproportionate lowering of the blood volume

The recurrent attacks separated by intervals of recovery suggested strongly that they were due to recurrent pulmonary emboli but no convincing evidence of pulmonary hypertension such as a loud P_2 deep cyanosis or right axis deviation developed The signs indicated myocardial involvement although the electrocardiogram did not show any progressive changes typical of myocardial infarction Myocarditis seemed unlikely as the heart was not enlarged In view of the persistent fever and leukocytosis in the presence of an aortic valvular lesion it seemed possible that the patient had a complicating bacterial endocarditis and that the myocardial disturbance was the result of repeated coronary emboli

Autopsy revealed multiple small myocardial infarcts resulting from

coronary emboli There was however no evidence of bacterial endo carditis and the source of the emboli was not evident There was a calcific aortic stenosis

This then was an example of circulatory insufficiency with severe and persistent hypotension resulting from failure of the heart muscle The low cardiac output was caused by repeated small myocardial infarctions in a patient with a pre existing calcific aortic stenosis

Illustrative Cases

I

(#217590 Admitted December 12 1940 to April 8 1941
Died March 27 1947)

THIS 30-year old Negro laborer was admitted because of dyspnea and pain in the chest He had had frequent epistaxes and blood serologic test for syphilis was positive in 1935 In 1932 he had an arthritis of the left elbow which was thought to be tuberculous One year before admission he had noticed some swelling of the ankles toward the end of the day which had persisted Four months before admission night sweats developed with an occasional chill Five weeks before he felt feverish had some dyspnea on exertion and dull aching pain in his chest most noticeable during extreme exertion or when lying flat on his back Two days before admission he developed orthopnea and the following day had a shaking chill

PHYSICAL EXAMINATION on admission T 102 6 P 110 R 30 B P 120/70

The patient was a well nourished and well developed young Negro who was acutely ill He was moderately dyspneic and orthopneic There was no unusual venous distention A bulging of the precordial region was noted There was dullness at both lung bases posteriorly Scattered moist rales were heard over both bases and on the right there was diminution in breath sounds and in tactile fremitus The cardiac impulse was diffuse being maximal in the 5th interspace in the anterior axillary line The heart was enlarged to the right and to the left The rhythm was regular rate rapid The first sound at the apex was accentuated and snapping being followed by a rough blowing systolic murmur There was a low pitched murmur in diastole P_2 was accentuated The liver was moderately enlarged

COURSE IN THE HOSPITAL The day following admission a loud leathery to and fro friction rub was heard principally at the apex but also elsewhere over the pericardium Aspirin was given The temperature which was elevated became normal during the first two days in the hospital The aspirin was decreased at this time which was followed by rise in temperature which again disappeared when the dosage was increased The friction rub persisted for four weeks Two months after admission auricular fibrillation developed Observers described a systolic murmur and thrill

at the base transmitted into the vessels of the neck interpreted as due to the presence of aortic stenosis At the time of discharge temperature and sedimentation rate were normal

LABORATORY DATA The hemoglobin was 13 4 gm leukocyte count was 13 000 with 62% polymorphonuclears 22% lymphocytes 16% mono cytes Sedimentation rate was 24 Urine showed an occasional trace of albumin and of sugar The blood serologic test for syphilis was negative Blood cultures were sterile Venous pressure was 120 mm of water

X ray examination on admission showed a tremendously enlarged heart with a somewhat triangular configuration A note on January 29 stated the heart was much enlarged particularly the left auricle Change in con tour of the heart when the patient was in the prone position would suggest the presence of some fluid in the pericardium A further note on February 17 stated that the heart was enlarged in all diameters Pulsations were vigorous X ray of the chest on April 4 still showed the heart enlarged in all diameters with convexity of the left border particularly in the upper portion The left lung where seen appeared clear but there was a dense consolidation in the right mid lung zone probably involving the middle lobe

Numerous electrocardiograms were taken During his early period in the hospital the only feature of note was a prominent P wave in lead 2 Records taken after February 21 showed auricular fibrillation and occa sional ventricular extrasystoles

SUBSEQUENT COURSE No change of note occurred until March 1946 when the patient was seen because of increase in dyspnea During the intervening years he had had bouts of dyspnea and orthopnea lasting for months at a time and relieved by prolonged rest There was still auricular fibrillation The heart was enlarged both to the right and to the left The blood pressure was 125/80 A presystolic murmur was heard at the apex There was a pronounced palpable pulsation systolic in time in the 3rd and 4th interspaces 4 cm to the right of the sternum Flatness to percussion over the same area extended into the right axilla X ray examination revealed consolidation of the right middle lobe

On December 4 1946 a right hemiplegia developed Examination on December 26 1946 showed absent knee jerks On January 15 1947 he had distended neck veins with moist rales at both lung bases The liver was enlarged Auricular fibrillation was present There was a rough systolic murmur loudest over the aortic area but heard throughout the precordium and transmitted to the vessels of the neck A systolic thrill was felt over the base of the heart The mitral first sound was followed by a short systolic murmur and a rumble was heard in diastole Fluoroscopic examination revealed a mass extending from the mediastinum to the right which did not appear contiguous with the right heart border With barium swallow the esophagus was not deviated The mass seemed to arise from the ascending aorta It was stated that definite pulsations could be seen in that mass It should be noted that blood serologic test for syphilis in January 1935 was positive with a titer of 12 units Final note was made on March 27 1947— patient dead on arrival at the hospital

DISCUSSION There seems little doubt that this patient had valvular heart disease and possibly also a congenital cardiac lesion There was an acute pericarditis at one stage of the illness, and febrile episodes suggesting acute rheumatic fever apparently responded to salicylates During the last year of life the patient developed what was interpreted as consolidation of the middle lobe had a pulsating mass which was thought to originate from the ascending aorta and also developed a hemiplegia It seems doubtful that one can logically account for all of these diverse manifestations by the natural evolution of a single disease process

During his hospitalization and in the seven years following there were numerous descriptions of the cardiac murmurs There were as many variations in these murmurs as there were observers who described them The shape of the heart the presence of an apical diastolic murmur in the absence of conspicuous aortic insufficiency, the enlargement of the left auricle and the enormous P waves in the electrocardiogram before the onset of auricular fibrillation are indicative of a mitral valve lesion The subsequent development of a basal systolic murmur and thrill with transmission to the carotid vessels, accompanied by x ray evidence of left ventricular enlargement suggested involvement of the aortic valves These findings together with an acute pericarditis appearing during the febrile episode which responded to salicylates suggest that he had chronic rheumatic valvulitis He may have been experiencing an exacerbation of rheumatic fever when first seen in 1940 In such a setting the development of auricular fibrillation would be natural When one couples this with the subsequent history of exacerbations and remissions in the signs of cardiac insufficiency for a period of over seven years one has a very strong case for rheumatic heart disease This type of cardiac disease is often complicated by release of mural thrombi which could explain the probable embolic episodes The development of the huge pulsating mass projecting almost to the right axillary region would be difficult to explain on the basis of rheumatic heart disease alone The additional possibilities seem to fall into two categories those which might be expected to evolve as a complication of rheumatic heart disease and those which might result from some other type of heart disease either alone or in association with rheumatic heart disease

The patient had a precordial bulge in 1940 suggestive of long standing cardiac involvement There was a big globular shaped heart with x ray evidence of auricular enlargement The murmurs were

strange and their character would lead one to suspect that a single valvular lesion alone did not suffice to explain all the changes described There was no right axis deviation in the electrocardiogram but the development of the systolic murmur and thrill at the base without the peripheral signs of aortic stenosis suggests the possibility of an auricular septal defect In the syndrome described by Lutembacher in which the presence of a patent interauricular septum is made evident clinically by the presence of mitral stenosis auricular fibrillation is commonly seen and there may be aneurysmal dilatation of the pulmonary arteries The prominence of the pulmonary conus on the left and the development of the right sided pulsating mass might be explained on this basis

There is one other complication of rheumatic cardiac disease which must be kept in mind primarily because of the extreme degree of cardiac enlargement—adhesive mediastino pericarditis The patient had a severe and persistent acute pericarditis but there were no physical signs described later which point clearly to the development of adhesions between the chest and the heart except possibly the visible impulses to the right of the sternum

He had syphilis with involvement of the nervous system If he had syphilis of the aorta and the pulsating mass was an aneurysm arising from the ascending aorta how can one account for the other features of his illness? A primary syphilitic myocarditis might have been the cause of heart failure in which event variable murmurs might be heard The pericarditis might be difficult to explain unless there was myocardial infarction associated with involvement of the coronary ostia Of course the pericarditis might have been tuberculous—a possibility that was seriously entertained in 1940 However there is little concrete evidence to support either suggestion

Coronary thrombosis on an arteriosclerotic basis is seen even in this age group It could explain the pericarditis and conceivably the pulsating mass as a cardiac aneurysm but this seems highly unlikely as there was no mention of paradoxical pulsation in the fluoroscopic report

Also one must not leave out the possibility that the pulsation observed was transmitted and that this mass was not vascular in origin but was a tumor of some type However this seems unlikely as systolic pulsations were seen on the chest wall to the right of the sternum

As another possibility this mass might have been associated with some congenital defect of the pericardium with effusion and transmission of the impulse

Of these various possibilities the two most likely ones seem to be
(1) Rheumatic heart disease with aortic and mitral involvement and possibly adhesive mediastino pericarditis,
(2) Lutembacher s syndrome with pulmonary artery aneurysm

ANATOMICAL DIAGNOSIS (Autopsy No 20505) Chronic rheumatic heart disease involving mitral tricuspid and aortic valves left auricular endocardium pericardium and aortic adventitia Perivascular scarring in right and left ventricular myocardium Remains of Aschoff bodies in left auricular endocardium and myocardium Fibrous pleural pericardial and peritoneal adhesions Cardiac dilatation and hypertrophy Chronic passive congestion Cirrhosis of the liver Scarring of meninges History of transient right hemiplegia Focal hemorrhages in lung pericardium and pelvic serosa History of sudden death

Both pleural cavities as well as that of the pericardium were completely obliterated by old fibrous adhesions The heart weighed 1100 gm and showed enlargement of all chambers The posterior tricuspid leaflet was extensively scarred and contracted and pulled down against the ventricular endocardium The left auricle was dilated and hypertrophied The mitral valve had deformed leaflets and was so scarred as to produce stenosis as well as insufficiency The middle aortic cusp at its base was thickened and contracted The mediastinal structures aside from adhesions which partially obliterated the various planes of cleavage were normal The presence of adhesive mediastino pericarditis undoubtedly played a major role in the mechanical difficulties against which the heart had to work

SUMMARY This 30 year old Negro laborer was first seen at age 23 with a febrile illness evidence of valvular heart disease and an acute pericarditis He was placed on aspirin and hospitalized for four months during which time auricular fibrillation developed The heart remained very large and a precordial bulge was noted Exacerbations and remissions of cardiac insufficiency occurred over several years Examination at age 29 again revealed a very large heart vigorous systolic pulsation to the right of the sternum auricular fibrillation evidence of aortic and mitral valve involvement and a pulsating mass thought to arise from the ascending aorta Autopsy revealed CHRONIC RHEUMATIC HEART DISEASE with involvement of aortic mitral and tricuspid valves The cause of the very large heart and the curious findings on fluoroscopy during life was adhesive mediastino pericarditis which undoubtedly had created a major mechanical burden for the heart

II

(#U50554 Admitted August 2 1933 Died August 3 1933)

THIS 41 year old Negro laborer was admitted with the complaint of short ness of breath for one week In 1925 he had pain in both ankles and up both legs for three weeks He was ambulatory throughout the illness and had no fever He had many sore throats at the age of 4 and 5 but none since In 1915 he had a urethral discharge for two days

The patient did heavy laboring work until 1931 when he became aware of a feeling of heaviness in the lower portion of his abdomen and his appetite diminished Six months before admission while driving a truck he suddenly became short of breath After two hours he felt well At about this time nocturia four or five times a night began

During the succeeding months similar attacks of shortness of breath appeared with increasing frequency lasting only a few hours Sometimes they were associated with exertion but quite often came on during sleep Five months before admission his blood pressure was found to be 160/110 The heart was enlarged to the left There were no murmurs There was accentuation of the aortic second sound and the arteries felt thick and rubbery The blood counts were normal The urine showed specific gravity of 1 025 trace of albumin and numerous red and white blood cells but no casts The nonprotein nitrogen was 26 mg / Phenolsulfonphthalein excretion was 65% in two hours A chest x ray showed the aortic shadow to be 6 5 cm in width and the left cardiac border was 10 5 cm from the midline Changes in the lungs at the left base were thought to be secondary to his cardiac condition

Three weeks before admission while sitting quietly he felt pins and needles crawling from his left elbow to his left hand The forearm felt numb and heavy and although he could move his hand his fingers and wrist felt weak His tongue seemed to be twisted and his speech was clumsy This episode passed off in a few days and he had no further symptoms of this sort

During the two weeks prior to entry the dyspnea was more severe and persistent A week before admission severe dyspnea necessitated his sitting upright both day and night This attack lasted up to the day of admission At times it seemed as though he were choking to death

PHYSICAL EXAMINATION on admission T 101, P 146 R 46 B P 178/148 in the right arm and 180/146 in the left arm

The patient s breathing was Cheyne Stokes in type and during phases of dyspnea he was acutely uncomfortable His expression was one of great

anxiety and there was marked cyanosis of his lips and mucous membranes During examination he vomited twice He perspired copiously The eyes showed pinpoint pupils (morphine) The fundi revealed narrow arterioles with arteriovenous nicking The percussion note was normal There were bubbling rales at both lung bases The breath sounds were normal in quality The point of maximal impulse was diffuse extending 13 cm to the left of the midline The rhythm was regular Both the first and second sound had a snapping quality There was a systolic blow at the apex not transmitted to the axilla No diastolic murmurs were heard The peripheral arteries were moderately thickened The liver extended below the level of the umbilicus There was no clubbing or edema The neurological examination was not remarkable

LABORATORY DATA Wassermann test was negative Red blood count 4 million and hemoglobin 86% Leukocytes 10 200 with normal differential Sickling negative Urine was clear amber strongly acid with specific gravity 1 030 albumin 4 plus 2 white and 2 red cells per high power field and occasional granular casts Blood culture showed no growth

COURSE IN THE HOSPITAL The patient was in the hospital 24 hours before death The temperature rose from 101 to 104° Venesection of 500 ml was performed and digitalis was given Numerous extrasystoles were heard during the last 12 hours Pulse rate decreased from 140 to 90 The rales in the lungs became less marked During the last four hours the patient became delirious the rhythm became irregular and the beats varied in strength Death occurred very suddenly

DISCUSSION (by Dr Elliot V Newman) *At first glance this would* seem to be a case of hypertensive heart disease with progressive cardiac failure The patient had a mild diastolic hypertension when first seen and quite marked diastolic hypertension when admitted to the ward five months later The hypertension however was not necessarily the cause of the cardiac failure During certain types of cardiac failure a diastolic hypertension may appear the pressure returning to normal as improvement in cardiac function is achieved Among these types may be mentioned those due to constrictive pericarditis or pericardial effusion and that occurring occasionally in the early stages of myocardial infarction More pertinent to the problem in this case is the type of rapidly progressive cardiac dilatation and failure caused by diffuse myocardial disease which is commonly associated with some diastolic arterial hypertension It seems quite paradoxical that a dilated failing heart with low output should maintain an elevated diastolic arterial pressure and there is no ready explanation in physiological terms for this situation The relation of the hypertension to the cardiac dilatation and failure can be clearly seen clinically in some cases when they appear and disappear simultaneously

The failure in the present case may be due to any of a number of different processes In a Negro man of this age syphilitic myocarditis may produce such a picture These patients have large dilated hearts progressive cardiac failure and often mild diastolic hypertension with no evidence of valvular defects There is frequently an apical systolic murmur as in this case this is interpreted as being due not to valvular disease but to dilatation of the mitral ring Or the failure might be due to diffuse myocardial damage secondary to coronary arteriosclerosis A similar clinical picture might result from myocarditis caused by a virus infection or from so called idiopathic myocarditis where there is diffuse damage of the heart muscle without any etiological explanation

The facts here suggest that the hypertension is not secondary to heart failure and also that this is not a case of simple hypertensive cardiovascular disease The greatest objection to the diagnosis of primary myocarditis is the level of the diastolic hypertension Usually the diastolic pressure level is not above 110 to 115 in cases of failure due to myocarditis In this case the values were 140–150 This makes one consider four other explanations for the hypertension (1) that the patient had hypertensive disease in addition to myocardial disease (2) that he had a pheochromocytoma (3) that the hypertension was related to renal damage from emboli or (4) that the hypertension was part of a generalized vascular disease such as periarteritis nodosa which also caused heart muscle damage

The transient cerebral symptoms and red cells and albumin found in the urine on two occasions lend support to the idea that there were emboli It is common for cases of myocarditis in failure to have embolic complications from thrombi formed in the heart cavities In this instance one might explain the hypertension in part on the basis of renal damage The attacks of dyspnea could have been the result of paroxysmal hypertension due to a pheochromocytoma Also in support of this is the very rapid pulse the pronounced sweating and the great anxiety However severe failure with marked cardiac enlargement is an unusual result of pheochromocytoma Generalized periarteritis could explain the hypertension fever renal damage myocardial failure and even the cerebral symptoms

In conclusion much of the picture in this case is consistent with syphilitic myocarditis but the negative Wassermann and the level of diastolic pressure deter one from making this diagnosis It is possible that the cardiac damage was on an arteriosclerotic basis with diffuse myocardial scarring and that the cerebral renal and hyper

tensive abnormalities and even some of the respiratory embarrass ment were due to emboli from the heart cavities However general ized arteriolar disease due to periarteritis seems to offer the best explanation of all of the major findings

ANATOMICAL DIAGNOSIS (Autopsy No 13256) Tumor of the adrenal medulla right arteriosclerosis arteriolosclerosis cardiac hypertrophy and dilatation pulmonary edema emphysema chronic passive congestion diphtheritic colitis

The heart weighed 630 gm The right auricle was distended and on opening the heart it was obvious that the right ventricle was also dilated The left ventricle was very much dilated and hypertrophied The arch of the aorta had some fine yellowish plaques suggesting sclerotic change The right adrenal was involved in a large circumscribed mass weighing 110 gm and measuring 6 cm in greatest diameter On section the mass was very nodular and lobulated There was a small bit of adrenal tissue still present at the lower pole of this large mass No metastases were found The tumor tissue was composed of large brown chromaffin cells with dark stained nuclei The organs showed hyaline arterioles

Nothing was found to explain the hematuria or albuminuria—the kidneys were perfectly normal The brain was not examined The heart was recorded in the protocol as the largest on record from a pheochromo cytoma case

SUMMARY This 41 year old Negro laborer had a story of severe attacks of dyspnea occurring over a period of six months They grew progressively more severe lasted for several hours and were accompanied by sweating and anxiety He had a very large heart hypertension and the evidences of severe cardiac insufficiency with dyspnea cyanosis pulmonary edema and hepatomegaly Urinary abnormalities were noted He had an attack suggestive of a cerebral accident He died suddenly after developing an irregular pulse with beats varying in intensity Autopsy revealed a typical PHEOCHROMOCYTOMA There were arteriosclerosis and arteriolo sclerosis The most striking feature was the very marked cardiac hyper trophy

III

(#382445 Admitted November 26 1946 Died December 6 1946)

This 35 year old ex service man complained of dyspnea cough and bloody expectoration There was no history of polyarthritis epistaxis or severe sore throats In 1944 while in the Army he had a penile lesion The serologic test for syphilis was positive and he received penicillin He had an appendectomy in 1944 and a few weeks later had sudden onset of pain in the chest accompanied by severe sweats The pain was aggravated by respiration and by cough After three weeks hospitalization he was discharged to full duty Nine months later he had a recurrence of the same type of pain which lasted for three days Subsequent to this he had a few minor episodes of pain which seemed pleuritic in type

In December 1945 he had one episode of paroxysmal nocturnal dyspnea with smothering sensations relieved by getting into an upright position Shortly after this he fainted after suddenly running up the stairs recovered in a few moments but felt dizzy and weak and shortly thereafter fainted again Mention was made that he had a heart murmur at that time After that episode there was mild exertional dyspnea and intermittent orthopnea In January 1946 soreness and swelling of the right leg developed dyspnea became more severe and there was a recurrence of his so called pleurisy This led to hospitalization for six weeks during which time he made a good recovery However on discharge he continued to have dyspnea on exertion and there was intermittent swelling of both legs and occasional distention of the abdomen There were milder episodes of pleurisy during the next few months and an exacerbation of orthopnea dyspnea and ankle edema led to a second period of hospitalization in August 1946 After discharge the edema and pulmonary symptoms continued although he felt comfortable while at rest in bed Three days before the present admission he noted the onset of cough with grossly bloody sputum chilly sensations and severe night sweats with increase in dyspnea and orthopnea

Physical Examination on admission T 99 P 72 R 24 B P 118/85

The patient s respiratory rate was increased There was no cyanosis The cervical veins were distended as were the superficial veins of the legs Beneath the clavicle on either side there was obvious venous pulsation There was minimal ankle edema Pupillary reactions were normal Ophthalmic examination was normal Fine and medium inspiratory and expiratory rales were present under the right clavicle high in the right axilla and near the scapular spine on the right There was a pleural friction rub over the right chest Examination of the precordium showed

a double cardiac impulse With systole there was a pulsation in the 4th intercostal space and a simultaneous retraction in the 5th intercostal space There was no Broadbent sign The point of maximal impulse was not forceful and no shock or thrill was felt There was dullness 10 cm to the left in the 5th interspace and 3 cm to the right in the 4th There was an occasional extrasystole At the apex there was a harsh systolic murmur maximal about 5 cm to the left in 5th interspace A protodiastolic gallop was present P_2 was greater in intensity than A_2 There was a paradoxical pulse There was moderate ascites The liver was enlarged but did not pulsate The right leg was larger than the left There was no calf tenderness Reflexes were physiological

COURSE IN THE HOSPITAL Because of the area of consolidation in the right upper lobe and the finding of a type III pneumococcus in the sputum the patient was started on penicillin He was also given digitalis There was no dramatic response The temperature fluctuated ranging around 100 to 101 There was no conspicuous lowering of the venous pressure During the second week in the hospital the fever increased The right leg remained swollen but there was no evidence of any acute process there Dyspnea and orthopnea increased and the relief which followed phlebotomy lasted for only a short time The patient coughed up blood tinged sputum The night of death he became increasingly restless and dyspneic complaining of severe pain in the right chest Blood pressure was 90/70 and further phlebotomy seemed inadvisable The patient suddenly began to vomit and became cyanotic and then comatose

LABORATORY DATA Hematocrit 53 hemoglobin 16 gm sedimentation rate 13 mm per hour Leukocytes 9 840 with normal differential, the highest white count during admission was 12 900 Blood serologic test for syphilis was negative Nonprotein nitrogen 64 mg % fasting blood sugar 100 mg % CO_2 21 6 mEq chlorides 107 mEq total serum protein was 6 88 gm % with albumin 4 63 gm % Alkaline phosphatase activity 4 7 units cholesterol 118 mg % bromsulfalein retention 52% after 30 minutes Serum bilirubin 3 7 mg % total 2 3 mg % direct prothrombin time 29 seconds 40 % of normal

Several blood cultures showed no growth Second strength tuberculin reaction was negative at 48 hours Venous pressure on admission 235 mm water Circulation time 30 seconds (Decholin)

The electrocardiogram showed marked right axis deviation X ray examination of the chest on November 26 showed a large area of pneumonic consolidation in the base of the right upper lobe also a small area of infiltration near the costophrenic angle on the right Heart and aorta were within normal limits

DISCUSSION This patient was in heart failure and the elevation of venous pressure and enlargement of the liver with ascites together with the marked right ventricular preponderance in the electrocardiogram suggest that the greatest strain was on the right side of the heart Systemic hypertension was never observed and in the absence of significant cardiac enlargement it seems probable that disease of

the myocardium was not primarily responsible This leaves several other possibilities which are outlined below The differentiation between them involves careful evaluation of all of the events which took place during the entire course of the patient s illness

A Congenital heart disease
  (1) pulmonic stenosis
  (2) interventricular septal defect

B Obstruction of the pulmonary circulation
  (1) pulmonary hypertension
  (2) primary obliterative disease of the pulmonary arteries
  (3) multiple pulmonary emboli with chronic cor pulmonale

C Valvular heart disease
  (1) mitral stenosis
  (2) tricuspid valve disease

D Interference with the return of blood to the heart due to
  (1) chronic constrictive endocarditis
  (2) chronic constrictive pericarditis

Congenital heart disease does not seem a very strong possibility A marked right ventricular preponderance always suggests pulmonic stenosis but such patients rarely reach this age without symptoms The absence of conspicuous cyanosis or clubbing and the presence of a loud pulmonic second sound seem to eliminate this possibility A patent interventricular septal defect is not likely in view of the absence of the typical murmur and the marked right axis deviation A slight septal defect may show none of the classic findings and if it were the seat of secondary bacterial implants might conceivably produce this clinical picture

Primary pulmonary hypertension results from obstruction to the arterial blood flow and may be due to sclerotic changes in the arteries emphysema pulmonary fibrosis or thrombosis of the pulmonary artery A sequel to the hypertension is enlargement of the right ventricle which the evidence leads one to believe was present in this case The pulmonic second sound is accentuated and the systemic pressure is usually low with low pulse pressure as was also found here The signs of failure are primarily those of failure of the right ventricle with venous distention liver enlargement ascites and edema

With extensive involvement of the pulmonary arteries as in Ayerza s disease marked cyanosis is a striking feature This is also true in cases of diffuse pulmonary disease such as acute diffuse interstitial fibrosis Cyanosis was never an outstanding feature here until

terminally, and diffuse changes were never described in the lungs on physical examination or roentgenography

The possibility that this patient had recurrent pulmonary embolism with the production of chronic pulmonary obstruction merits further discussion There was a history of repeated episodes of chest pain of a pleuritic type over a period of two years The first of these appeared only a few weeks after appendectomy In the beginning there was no associated dyspnea but this developed later In the final episode after evidences of cardiac insufficiency had been present for some time there was dyspnea hemoptysis and jaundice In January 1946 persistent swelling of the right leg developed followed by a recurrence of the chest pain During the final phase of the illness it seems inescapable that the patient had pulmonary embolization This may have arisen from a cardiac mural thrombus but there was better evidence of femoral venous thrombosis It seems worth while to discuss some of the clinical aspects of this problem at this point *Pulmonary emboli* may occur without producing the typical picture described in most textbooks They are now recognized by symptoms and signs which were often regarded in the past as indications of primary disease of the heart and lungs or as commonplace complaints having no special significance One must use the evidence from several sources to make the diagnosis Thoracic symptoms and signs may be expected in about half of the cases Pain is the most frequent symptom and is usually pleuritic in character, although it may be substernal and accompanied by a sensation of smothering or constriction Cough is less specific but is most significant when combined with hemoptysis Dyspnea occurs in severe cases especially when there are other evidences of right sided cardiac embarrassment However orthopnea is usually conspicuously absent In the presence of limited cardiac function as in this man jaundice often follows the development of an area of infarction

The symptoms and signs of *thrombosis in the leg veins* should be sought with particular care when there is no evidence to indicate that the emboli arose from the heart There is no endeavor which pays greater rewards for diligence The signs are more easily seen against a background of preliminary routine observation by comparative measurements of leg circumference There may be some pain in the affected leg and tenderness which the patient localizes deep in the tissues The tendency to resist dorsiflexion of the foot is important General symptoms such as unexplained elevation of the pulse rate and temperature are important X ray and electrocardiographic al

terations may be helpful With such aids to diagnosis available the correct diagnosis can be made in a surprisingly large proportion of the cases by the alert clinician

Unfortunately thrombosis in the veins of the legs or pelvis is not always accompanied by evidences of venous obstruction It may be quiet for long periods and only disclose its presence by releasing emboli These may develop in young active people who seem healthy in all other respects The story here is compatible with the concept that this man had phlebothrombosis with multiple pulmonary emboli The nature of the disturbance became obvious clinically only with the onset of swelling of the right leg and with the development of progressive obstruction of the pulmonary arterial bed leading finally to the clinical picture of severe right heart strain

Rarely *primary tumors* develop in the heart chambers These are usually seen in the left auricle but a primary tumor in the right auricle could conceivably explain many features of this picture Syncope after exertion may be due to sudden blocking of the auriculoventricular orifice by the tumor However these tumors are unusual are rarely seen on the right side of the heart and in this instance would not explain many of the other clinical features

Mitral valve disease seems to be reasonably excluded by the absence of the usual findings on cardiac examination However the murmur may be very localized and easily overlooked unless one listens in the precise area with the patient in the proper position

Tricuspid valve disease sufficient to produce this degree of cardiac change is very rare and is almost never seen in the absence of clinical evidence of involvement of the mitral or aortic valve Mural thrombi could form with resulting pulmonary emboli or an acute superimposed vegetative endocarditis could account for the later features It should be pointed out that in patients with tricuspid stenosis the circulatory phenomena associated with inflow stasis as seen in constrictive pericarditis may occur These may be due not to myocardial insufficiency but to mechanical obstruction and as a result they may persist in spite of rest and digitalis Distinct peripheral venous pulsation and liver pulsation were not clearly present here and as has been pointed out before it is dangerous to place reliance on auscultatory phenomena in diagnosing tricuspid valve disease In the presence of increased pulmonary resistance with right sided failure functional tricuspid insufficiency may occur

The other major possibility is that this patient had *constrictive pericarditis* The clinical syndrome produced by inflow stasis due to

inability of the heart to expand normally is fairly characteristic Dyspnea, enlargement of the abdomen, and edema of the feet are the common symptoms Fever night sweats and other features indicative of infection may be prominent if the pericarditis is due to tuberculosis Two signs are uniformly present—enlargement of the liver and engorgement of the jugular veins The size of the heart is usually normal and murmurs are the exception Blood pressure and pulse pressure are low and there is frequently a paradoxical pulse as in this case Venous thrombosis and pulmonary emboli are not usually seen and any marked axis deviation in the electrocardiogram would be most unusual To explain this one probably would have to postulate localized constriction about the pulmonary veins Polyserositis might explain the recurrent episodes of pleuritic pain and form the basis for the pericarditis If the patient had tuberculous pericarditis the terminal features with pulmonary involvement and hemoptysis might be on the basis of pulmonary tuberculosis and not due to emboli at all Tuberculin tests were negative and no tubercle bacilli were found in the sputum

I conceive of this patient as having no primary disease of his heart The most logical reconstruction of this clinical picture seems to be as follows

Quiet phlebothrombosis developed in 1944 probably after appendectomy followed by several small emboli which left no clinical residual A large embolus occurred in December 1945 accounting for the first severe sudden attack of dyspnea Perhaps part of this lodged in the auricle leaving a small ball valve thrombus which after sudden exertion blocked temporarily the auriculoventricular orifice resulting in sudden collapse

The venous thrombotic disease revealed its presence in January, 1946 with pain and swelling of the right leg

By this time the obstruction to the pulmonary vascular bed was sufficient to result in increasing dyspnea and other signs of right ventricular failure

Subsequent emboli produced infarcts because of the presence of cardiac failure and the symptoms were accordingly more severe With the last episode of infarction hemoptysis occurred The increased red cell destruction in the presence of a congested liver resulted in jaundice

The course of the illness and the marked right ventricular preponderance in the electrocardiogram would lead one to expect hypertrophy of the right ventricle

ANATOMICAL DIAGNOSIS (Autopsy No 20301) History of swelling of right leg Organized recanalized thrombus of right femoral vein Organized massive pulmonary emboli to right and left main pulmonary arteries Old and recent infarcts of lungs Hypertrophy and dilatation of right ventricle and auricle Chronic passive congestion of liver pancreas and spleen

The heart was slightly enlarged and globular in shape The right ventricle was definitely hypertrophied and dilated and the dilatation was most apparent about the pulmonary conus Massive thrombus material filled the main pulmonary artery There were wedge shaped rusty scars suggesting old infarcts A large fresh hemorrhagic infarct bulged out posteriorly at the lower part of the right upper lobe and a smaller fresh infarct was found in the right lower lobe There was extreme nutmeg mottling of the liver

The section from the right femoral vein showed a remnant of an organized recanalized thrombus containing hemosiderin In the main branches of the pulmonary artery there were old thrombi partly organized with recanalization and hyalinization There were a number of infarcts of various ages in the lungs It seemed clear that the heart failure resulted from the obstruction of the pulmonary arteries and that this obstruction represented emboli from the femoral vein

SUMMARY This 35 year old male had recurrent episodes of pleuritic pain beginning a few weeks after appendectomy More than a year later he had an episode of severe paroxysmal dyspnea followed by an attack of syncope with exertion Progressive right sided heart failure ensued and swelling of the right leg developed Examination showed severe venous hypertension signs of consolidation in the lungs a systolic murmur without conspicuous cardiac enlargement jaundice hepatomegaly and ascites Electrocardiography revealed right axis deviation The patient had fever and coughed up bloody sputum before his sudden death which followed a severe attack of thoracic pain Autopsy revealed heart failure with right sided hypertrophy due to OBSTRUCTION OF THE PULMONARY CIRCULATION BY EMBOLI from the periphery The lungs showed infarcts of various ages During the past few years a number of cases of this type have been seen in this clinic

IV

(#261688 First admission June 28 1942 to July 8 1942
Final admission August 2, 1942 Died August 15 1942)

THIS 40-year old white mechanic was discovered to have Addison s disease while being treated for tuberculosis of the lumbar spine in another hospital Pellets of desoxycorticosterone were implanted and by variation of salt intake he was able to remain free of symptoms An x ray of his chest taken in May 1942 showed the heart and aorta to be normal but revealed an opacity near the horizontal fissure on the right which was thought to represent a small collection of fluid There was thickening of the pleura at the right base

The day prior to admission in June 1942 he developed coryza followed by sore throat causing some difficulty in breathing but no chest pain He began to vomit felt weak and drowsy and noticed numbness of his feet He was found to have a temperature of 104 pulse rate 110 respirations 22 blood pressure 138/90 There was typical Addisonian pigmentation The pharynx was bright red but there was no exudate The uvula was swollen and there were tender enlarged glands at the angles of the jaw Examination of the chest showed slight diminution of breath sounds over the right lower lobe The heart was slightly enlarged to the left The sounds were loud and there was a blowing systolic murmur at the base He remained for twelve days and showed rapid improvement X ray showed that the area of opacity previously described in the mid portion of the right lung had extended but still appeared to represent interlobar fluid His blood pressure was 128/104 at the time of discharge

On July 30 he noted some edema of the ankles and discontinued his salt intake On August 2 he awoke with a sore throat and complained of pain in the chest That evening his temperature was elevated and he had a shaking chill The precordial pain gradually increased in severity

PHYSICAL EXAMINATION on admission T 103 6 P 132 R 22 B P 112/90

The patient was thin and moderately dehydrated The pharynx was injected tonsils were moderately enlarged but there was no exudate The lungs showed dry wheezes at the bases and over the right upper lobe anteriorly but no moist rales were heard The heart was normal to percussion No point of maximal impulse was seen or felt The sounds were normal in character and there were no murmurs The liver was not enlarged

COURSE IN THE HOSPITAL The first six days in the hospital the

patient s temperature ranged from 100 to 104 but after that there was no fever until a terminal rise to 103 8 He was placed on sulfadiazine and given sodium chloride and also adrenal cortical extract The second morning the blood pressure had fallen to 70/30 the pulse was feeble and rapid Intravenous saline and glucose were given in addition to large amounts of cortical extract Two days after admission he became dyspneic and the neck veins were distended Moist rales were noted at the right lung base Venous pressure was 260 mm of water He was digitalized rapidly and placed in an oxygen tent The blood pressure gradually rose to 160/84 and the venous pressure dropped moderately After a few days the dyspnea became less marked and he was finally removed from the oxygen tent He seemed better for several days but on August 13 complained of a sharp pain below the left nipple which was worse on inspiration The lungs were clear and no new findings were described on physical examination The blood pressure was 118/70 The following day he vomited several times and complained of severe pleuritic pain a pleuro pericardial friction rub was heard to the left of the sternum Blood pressure fell to 80/40 The venous pressure began to rise the extremities became cold and the breathing grew more difficult The heart sounds were distant and on August 15 the patient died the temperature having risen sharply during the last two days

LABORATORY DATA Hematocrit 36 sedimentation rate 14 mm per hour icterus index 7 leukocytes 15 800 Blood smear normal The day following admission nonprotein nitrogen wa 22 mg chlorides 115 mEq CO_2 54 1 vol % fasting blood sugar 67 mg % refractive index 5 3 gm / protein Serum sodium on August 5 was 127 1 mEq and on August 10 128 8 mEq On August 14 serum sodium was 135 8 mEq and serum potassium was 5 6 mEq Cultures of throat venous blood and urine revealed no pathogenic organisms

On August 5 portable x ray of chest showed patchy clouding throughout lower half of right lung field probably due to an acute pneumonic process On August 10 the transverse diameter of the heart was markedly increased both to right and left Aorta was slightly dilated Marked clearing of diffuse process in right lower lobe There was still clouding in mid portion of right lung field probably due to interlobar fluid

DISCUSSION This patient had adrenal insufficiency with the typ ical clinical picture of Addison s disease There is no certain way of distinguishing clinically between cortical insufficiency resulting from atrophy and that secondary to tuberculosis of the adrenals Tuber culosis is responsible for destruction of the gland in about 70 per cent of the patients with hypoadrenalism There is rarely active pul monary tuberculosis but an associated involvement of the genito urinary tract or of the bones and joints by tuberculosis is more com monly seen This patient had evidence of tuberculous disease of a lumbar vertebra and also x ray findings suggesting a localized pleu ritis with effusion which may also have been caused by the tubercle

bacillus These facts not only help one in predicting the state of the adrenals found at autopsy but may be helpful in elucidating the circumstances responsible for the final Addisonian crisis and death

Patients with Addison s disease react to stress poorly, and what in a normal individual would be a minor incident such as an upper respiratory infection or a minor surgical procedure may result in a severe reaction culminating in a severe crisis which may prove fatal despite the best available treatment It has been observed that the duration of life is longer and these severe crises are less frequent in patients in whom pigmentation is an outstanding characteristic, and in whom asthenia and gastrointestinal symptoms are less marked This seems to be the case here and it is reasonable to assume that some added factor or complicating disease was responsible for the final fatal crisis

The interest centers about the changes in the lung and about the cause for the increase in the size of the heart and the elevation in venous pressure

There was no evidence of hypertension in either the pulmonary or systemic circuit to produce this sudden enlargement in cardiac size No murmurs were heard and there was no suggestion in the many examinations of either valvular or congenital heart disease

This leaves two main categories of heart involvement which must be considered in more detail—myocarditis and pericarditis

The point of maximal impulse was never seen or felt during the last admission but no gallop rhythm was present and the sounds were said to be normal in character In addition a pleuro pericardial rub was heard on one occasion This sequence of events might occur in the pancarditis of acute rheumatic fever, but onset of such an illness at this age with no preceding history of any of the manifestations of the rheumatic state would be unusual Acute myocarditis of unknown etiology—so called Fiedler s myocarditis—would be another possibility and precordial pain is often a prominent feature However, the evidence as outlined does not suggest myocarditis as a likely possibility with the possible exception of the limited improvement following administration of digitalis The presence of pain and the quiet precordium suggest coronary occlusion but the onset was gradual and the low blood pressure adequately accounted for by other factors

There were many features compatible with the presence of a pericardial effusion There was precordial discomfort and a friction rub was heard The venous pressure was high and the cardiac enlargement

Table 3 Diseases Causing Involvement of the Pericardium

I Acute pericarditis with or without effusion
- A Due to infection
  1. Tuberculous
  2. Pneumococcal
  3. Staphylococcal
  4. Tularemic
  5. Brucella
  6. Meningococcal
  7. Scarlatinal
  8. Acute benign (idiopathic)
  9. Amebic
- B Diseases of the rheumatic spectrum
  1. Rheumatic fever
  2. Systemic lupus erythematosus
  3. Rheumatoid arthritis
  4. Periarteritis nodosa
- C Metabolic or endocrine abnormalities
  1. Uremia
  2. Myxedema
  3. Addison s disease
- D Secondary to myocardial infarction
  1. Coronary thrombosis
  2. Coronary embolism
- E Neoplastic or granulomatous disease invasion
  1. Carcinoma of lung
  2. Carcinoma of stomach
  3. Lymphoma
  4. Sarcoidosis
  5. Leukemia
- F Hemorrhagic pericarditis
  1. Penetrating wound
  2. Rupture of dissecting aneurysm
  3. Rupture of mycotic aneurysm (subacute bacterial endocarditis)
  4. Rupture of syphilitic aneurysm (sinus of Valsalva)

II Chronic disease of the pericardium
- A Constrictive pericarditis (tuberculous pyogenic infection cause un known)
- B Adhesive mediastinopericarditis (secondary to rheumatic fever)

great to right and left In addition no point of maximal impulse could be seen or felt Several possible causes of such a pericarditis with ef fusion exist but in view of the presence elsewhere of lesions which were presumably tuberculous this seems the logical cause The lesion described in the region of the horizontal fissure on the right probably represented an old pleuritis also tuberculous in origin Thus the ab

sence of previous cardiac symptoms and the sudden appearance of manifestations suggesting pericarditis with effusion in an individual with Addison s disease and other probable tuberculous lesions suggest the following diagnoses

(1) Bilateral tuberculosis of the adrenals with hypoadrenalism
(2) Tuberculosis of the lumbar spine
(3) Tuberculous pleuritis
(4) Tuberculosis of the mediastinal lymph nodes with tuberculous pericarditis and fatal Addison s crisis

The lesions in the lungs which cleared somewhat during his hospital treatment were probably either the result of lobular pneumonia or less likely congestive changes secondary to the cardiac insufficiency

NATOMICAL DIAGNOSIS (Autopsy No 17995) History of Addison s
se for calcified tuberculous focus right lower lobe of lung Fibrocaseous
ease pressure both adrenals Pigmentation of skin Tuberculosis of 5th
erculo is no e iden Organizing fibrinous pericarditis with effusion Chronic
bar vertebra t to produc liver Polyserous effusions Pulmonary edema and
ve congestion ult idiazine treatment Casts in renal tubules and
asis History ere heard and light scarring of liver Marked generalized renal
ating epithelium ther valvular o Horseshoe kidney Anomalous renal arteries
onary arteriosclerosis ain categories of and thymus Chromophobe adenoma
ment of lymph detail—myocarditis ural and the peritoneal cavities In
is Right pleural nodes impulse was never ely obliterated by fibrous pleural
d was present in adhesions p rhythm was present encapsulated between the right
eural cavity the left ter In addition a pleurdium was very thick The
00 ml of which was his sequence of events date in places about 5 mm
ddle lobe fluid was large tic fever but onset of s Two calcified foci were
nous fluid The pericardial found story of any of the manife ormal On section no
dium was the seat of a parietal cavqual Acute myocarditis of issue with yellowish
astinal nodes seemed shaggy pericarditis—would be anothe bra had its centrum
The adrenals were harder normal prominent feature Howev which extended
vas visible only much gray than it myocarditis as a likely rked stenosis of
seous material The 5th lumbar fibrous ne limited improvement for ared to be two
by very soft caseous material verte esence of pain and the quie ry narrow
arteriosclerotic plaque in the aorta but the onset was gradual cells Th
e left coronary artery producing ma ly accounted for by other
ce of several millimeters There app with the presence of a peri
ide and the mouths of all four were comfort and a friction rub
only tiny islands of remaining adrenal the cardiac enlargement
and thick made up of fibrin and inflar
morphonuclear leukocytes were numer
similar pericarditis though les
17082 and 13434 which wer
which the cause was tubercu
se cases is as obscure
d white male
d a locul

a sore throat and precordial pain which precipitated an Addisonian crisis He improved temporarily but developed a pleuro pericardial friction rub The venous pressure was elevated and cardiac enlargement was present The clinical diagnosis was tuberculosis of spine adrenals pleura and pericardium with heart failure due to pericardial effusion At autopsy the pericardial sac was distended with clear fluid and there was a sterile FIBRINOUS PERICARDITIS There was a tuberculous pleurisy and TUBERCULOSIS OF THE ADRENALS Review of 20 cases of Addison s disease autopsied at the Johns Hopkins Hospital has revealed four cases with a sterile pericarditis of this type the precise cause of which is not known

V

(#230818 Admitted November 8 1942
Died November 12 1942)

THIS 30 year old Negro laborer complained of shortness of breath of four weeks duration At age of 14 he had gonorrhea At age 17 his Wassermann was positive and he received 12 arm and 12 hip injections He was hospitalized in 1935 because of a stab wound in the left chest following which a pneumothorax developed The heart was normal in size and no murmurs were described

He had no further difficulty until April 1941 when a dull aching pain developed in the lower abdomen At this time he had a cold with sore throat He then began to have migratory aching in his joints There was no local swelling of any joints at this time Within a brief period he developed progressive dyspnea on exertion and then at rest This was followed by orthopnea and bouts of nocturnal dyspnea He gradually became edematous and was first admitted May 29 1941 He was orthopneic dyspneic and moderately cyanotic There was edema of the legs and ankles Signs of fluid were present at the right lung base and there were moist rales throughout both lungs A systolic thrill was noted at the apex The heart was markedly enlarged to percussion and systolic and presystolic murmurs were described at the apex The pulmonic second sound was very loud The blood pressure was 100/75 The liver was moderately enlarged There was a positive serologic test for syphilis White count was normal as was the sedimentation rate Urine showed albumin white cells occasional red cells and casts Venous pressure was 175 mm of water He was placed on bed rest and limited fluids and was digitalized Serosanguinous fluid was withdrawn from the right pleural cavity Electrocardiogram showed a rate of 67 with low voltage in the three standard leads T1 was isoelectric T2 inverted T3 low and upright It was thought that these changes in the absence of digitalis administration indicated myocardial damage X ray of the heart revealed enlargement of the cardiac shadow in all diameters

He responded well to treatment and a few days after admission showed no evidence of valvular disease After discharge he continued to have evidence of cardiac insufficiency with dyspnea edema extrasystoles cough and upper abdominal discomfort In October 1942 he was noted to have auricular fibrillation The liver was markedly enlarged at this time The lungs were clear and there was no edema One week before the final admission he developed intermittent precordial pain with radiation to

both shoulders and some migratory arthralgia The day before admission he became nauseated vomited and developed a sore throat

Physical Examination on admission T 102 P 132 apical 128 radial R 36 B P 100/80

The patient was sitting up in bed in considerable respiratory distress There was a cough productive of small amounts of blood tinged sputum There was no cyanosis or edema The pulse felt very weak There was marked distention of the neck veins Pupils were small equal and slightly irregular Fundi were normal There was dullness to percussion at the right base posteriorly and in the right axilla with diminished fremitus and voice sounds There were many moist bubbling rales at the right base and finer crepitant rales at the height of inspiration over the remainder of the right chest The apical impulse was quite forceful diffuse rapid and irregular There was a systolic thrill at the apex There was a diastolic shock in the pulmonic area The heart was enlarged to the left with marked enlargement in the region of the pulmonic conus The sounds were loud P was accentuated There was a loud systolic murmur best heard in the mitral area A mid diastolic murmur was heard in the same region P_2 was split The cardiac outline did not seem to change with change in position The liver extended 5 fingerbreadths below the costal margin There was no ascites Knee and ankle jerks were sluggish

Course in the Hospital The patient was continued on digitalis given ammonium chloride and also treated with quinidine The auricular fibrillation continued On the third day he became drowsy and unresponsive and the area of cardiac dullness had increased He was cyanotic and definitely icteric The venous pressure varied from 240 to 260 mm water The heart sounds became poor in quality Temperature which was 102 on admission fell to subnormal On the fourth hospital day he was completely comatose and his cardiac rhythm was regular The blood pressure remained in the neighborhood of 95/70 The signs of pulmonary edema increased

Laboratory Data Blood serologic test for syphilis positive Specific gravity of the urine was 1 020 with 3 plus albumin numerous white cells an occasional red cell and rare cellular and granular casts Hemoglobin 15 2 gm hematocrit 50 icterus index 20 Leukocyte count 11 600 with marked shift to the left Nonprotein nitrogen was 62 mg % rising to 90 mg / before death chlorides 96 2 mEq CO_2-combining power 14 9 mEq on admission 18 3 before death total serum protein 6 85 gm / serum bilirubin 16 mg / direct reaction Blood culture was sterile Throat culture yielded normal throat flora with a predominance of pneumococci Electrocardiogram on November 9 Rate approximately 100 totally irregular rhythm QRS duration *0 10 sec Tendency to left* axis deviation QRS voltage quite low Ventricular complexes abnormal in shape suggesting origin of the ventricular rhythm from an idioventricular focus Auricles fibrillating

Discussion The basic problem is to determine the cause of the heart disease which led to death from cardiac insufficiency At no

time did the patient have systemic hypertension and congenital anomalies can be ruled out by the normal cardiac findings in 1933

All of the evidence here although the differentiation is often diffi cult suggests that the increase in heart size was the result of dilata tion rather than pericardial effusion There may have been some increase in pericardial fluid but the course of the illness suggests that this was not the important factor in the production of the cardiac failure There may have been secondary pulmonary hypertension as a consequence of mitral valve disease or multiple pulmonary emboli, but the facts do not lead one to suspect that elevation of pressure in the lesser circulation was the basic factor

It is often difficult to decide whether there is structural disease of the valves There were no murmurs described here which would allow one to say confidently that there was valvular disease there was no typical change in the quality of the pulse no characteristic configura tion of the heart or striking preponderance of the right or left ven tricle Associated manifestations of disease are always important con siderations and there was a story of migrating polyarthritis although the joints were apparently not red or swollen It is important to remember here that the signs of valvular disease disappeared almost completely when the patient recovered from the initial bout of cardiac insufficiency and that active rheumatic fever of this severity appear ing for the first time at such a late age would be unusual although the diagnosis of rheumatic heart disease was made consistently by those who saw the patient on the wards

Since the cause of the heart failure does not seem to fall into any of the five categories discussed one may assume that the patient had some type of myocardial disease This is supported by the course of the illness the massive cardiac enlargement with low pulse pressure and the electrocardiographic changes

The *causes of myocardial disease* may be divided into five main categories as outlined in Table 4

Of the inflammatory diseases reasons have already been given for the exclusion of rheumatic fever The other possibility is syphilis which will be discussed presently In the other categories the only one which seems to need further discussion is coronary arteriosclerosis

Arteriosclerotic heart disease is quite unlikely The age of the patient the absence of any evidence of arterial disease and the char acter of the symptoms are all strong points against it In the presence of a positive serological test syphilis seems more likely as the cause than Fiedler s myocarditis Not infrequently, in syphilitic patients

Table 4 Classification of Diseases Which Involve the Myocardium (Modified after Hamman)

1 Infections which may produce myocardial lesions
- a Rheumatic fever
- b Typhus fever
- c Diphtheria
- d Syphilis
- e Trichinosis
- f Sarcoidosis
- g Fiedler s myocarditis

2 Intoxication or hypersensitivity to chemical substances or drugs
- a Digitalis
- b Strophanthus
- c Sulfonamides

3 Disease due to nutritional defects or changes in the circulating blood
- a Beriberi
- b Sickle cell anemia

4 Changes secondary to inadequacy of the blood supply to the heart muscle
- a Coronary arteriosclerosis
- b Coronary embolism
- c Narrowing of coronary ostia due to syphilis

5 Myocardial involvement in the course of certain systemic diseases
- a Primary amyloidosis
- b Muscular dystrophy
- c Scleroderma
- d Periarteritis nodosa
- e Systemic lupu erythematosus
- f Hemochromatosis

who die of heart failure without evidence of aortic or coronary insufficiency there may be infiltration throughout the heart with a fine interlacing net of fibrous tissue These may be the only lesions found to explain the great enlargement of the heart and its failure Although it is difficult to demonstrate spirochetes in such cases everything else seems to point clearly to the myocardial lesions being due to syphilis The following features of syphilitic myocarditis as observed in other cases fit well with the observations in the present case

(1) The patient should have other evidence of syphilis
(2) The age of the patient is usually around 40 years or less while arteriosclerotic heart disease usually comes on at an older age
(3) The heart is greatly enlarged there may or may not be a systolic murmur
(4) Conspicuous in most cases is a low pulse pressure
(5) Once myocardial insufficiency develops there is never a really satisfactory recovery
(6) Transient hypertension is frequently observed during the periods of severe failure sudden death is common

The jaundice in the present case was probably the result of pulmonary infarction in the presence of a liver which had long been functionally impaired by chronic passive congestion The renal insufficiency seemed to have been a part of the chronic passive congestion

and circulatory collapse The fever and slight leukocytosis were probably the result of pulmonary infarction or lobular pneumonia

ANATOMICAL DIAGNOSIS (Autopsy No 18110) History of syphilis (positive Wassermann) Diffuse myocardial scarring Cardiac dilatation and hypertrophy Chronic passive congestion of lungs liver and spleen Jaundice Hydrothorax Hydropericardium History of auricular fibrillation Mural thrombi in right and left auricular appendages Healed tuberculous complex left apex Lobular pneumonia

The left pleural cavity contained 200 ml of yellow fluid and the right about 400 ml The pericardial cavity contained 200 ml of icteric fluid The heart was greatly dilated and slightly hypertrophied and weighed 430 gm

Microscopic sections revealed diffuse very fine scarring precisely like that seen in numerous other cases here in association with syphilis In the present case no fresh lesions were seen but in at least one other previous case fresh lesions with necrotic fibers and mononuclear cell infiltration were found together with the diffuse scarring There was nothing that suggested rheumatic infection and since these cases always occur in syphilitics it is reasonable to ascribe the damage to syphilis even though spirochetes cannot be demonstrated

SUMMARY This 30 year old laborer known to have syphilis since the age of 17 developed progressive cardiac insufficiency and died 18 months later There were signs of both right and left sided heart failure Conspicuous murmurs were present during failure but disappeared with improvement Auricular fibrillation developed The heart was enormously enlarged the pulse pressure was low and the sounds were of poor quality The various causes of myocardial disease were considered and a simple classification of them was presented SYPHILITIC MYOCARDITIS was considered to be the best clinical diagnosis Autopsy revealed fine diffuse myocardial scarring which has been encountered in numerous other cases of syphilis

VI

(#130132 Admitted March 14 1945 Died March 14 1945)

This 15 year old white Jewish schoolboy complained of cough sore throat and soreness of the neck of two days duration swelling and tenderness of the left ankle for six days and shortness of breath and weakness for 18 hours

During infancy he became obese and subsequently manifested the mental and physical retardation characteristic of true Frohlich s syndrome for which he was given various androgenic and follicle stimulating mate rials At age 6 after having measles he developed polyarthritis and a diagnosis of acute rheumatic fever was made He was placed on salicylates and after a month his symptoms disappeared On occasions thereafter slight enlargement of his heart was noted and a soft systolic murmur was heard in the mitral area

In January 1938 the heart was described as enlarged to the left P was louder than A_2 B P was 90/60 He was hospitalized in November 1939 with a diagnosis of probable rheumatic fever A systolic cardiac murmur was described

One month before his final admission he developed an eruption over the trunk which was accompanied by fever and sore throat The local physi cian made a diagnosis of measles but suggested the possibility of scarlet fever The boy recovered uneventfully and was well until 10 days before admission when he developed an upper respiratory infection which lasted a few days Six days before admission he complained of swelling and pain in the right ankle which slowly subsided He continued to have soreness of his throat and a feeling of stiffness in his neck On the evening of admis sion he became short of breath and was found to have a rapid pulse rate with normal temperature

Physical Examination on admission T 100 4 P 158 R 48 B P 156/95

The patient appeared acutely ill and coughed occasionally but produced no sputum The skin was flushed He was a short oddly proportioned fat boy with infantile hands and feet The obesity was distributed over the upper thighs the hips and the lower abdomen The eyes were normal in appearance and the fundi showed no changes The tonsils were large and the pharynx was diffusely inflamed There was edema of the pharyngeal wall and uvula and a patch of white exudate on the right tonsil Numerous small soft lymph nodes were palpable in the anterior cervical region but there was no generalized lymph node enlargement Respirations were labored with grunting expiration There was dullness to percussion over

the right upper lobe anteriorly and posteriorly The left lung was resonant throughout Over the area of dullness many fine and coarse rales were heard which did not disappear after cough The breath sounds were bronchial in character A faint cardiac impulse was present in the 5th interspace to the left of the nipple line There appeared to be no enlargement of the heart to the right The heart rate was very rapid but the rhythm was regular A presystolic gallop rhythm was heard at the apex In this area there was a high pitched rather loud systolic murmur late in systole Diastole was clear There was a minimal amount of edema of the legs The liver was palpable 3 fingerbreadths below the costal margin There was sparse growth of pubic hair feminine in distribution and the penis was small The testicles were atrophic The neck was supple

Course in the Hospital The pulse rate remained rapid and cyanosis developed The preliminary diagnosis was lobar pneumonia for which penicillin was given The patient became progressively more cyanotic despite being in an oxygen tent He was very apprehensive On one occasion he suddenly became intensely cyanotic and the chest filled with coarse bubbling rales thought to be due to acute pulmonary edema He continued to cough up more frothy sputum and to become progressively more cyanotic He vomited at intervals and his respirations became irregular He died a few hours after admission

Laboratory Data Hemoglobin 11 4 gm leukocyte count 21 000 sedimentation rate 32 mm per hour nonprotein nitrogen 49 mg % chloride 97 mEq /L CO_2-combining power 23 mEq Throat culture heavy growth of beta hemolytic streptococcus blood culture sterile

Discussion Before discussion of the various aspects of the final illness in this case it may be said that the patient was considered by competent endocrinologists to have the typical features of Fröhlich s syndrome

It seems quite evident from the course of events that this patient did not have a simple lobar pneumonia The rapid fluctuations in the cyanosis the evidence of pulmonary edema the hepatomegaly the gallop rhythm and extreme tachycardia suggest heart failure due to acute disease of the myocardium

Many acute infections are associated at one time or another with acute myocarditis due either to direct infection of the myocardium or to a toxin produced by the infecting organism One must always consider a diphtheritic etiology when the onset is sudden and preceded by a sore throat as in this case It is true that hemolytic streptococci were cultured from the throat but these organisms often coexist with diphtheria bacilli However the joint manifestations and the pulmonary consolidation would have to be explained on another basis Acute idiopathic myocarditis—so called Fiedler s myocarditis—must be considered but is very rare and in contrast to other

types is frequently associated with rather marked precordial discomfort

The clinical picture into which this case seems best to fit is that of a fulminating acute rheumatic fever There was a history of previous migratory polyarthritis followed by questionable cardiac involvement There had been a recurrence of the joint involvement several years after the initial episode The patient developed a sore throat and had a rash which was thought to resemble scarlet fever—a not uncommon precursor of active rheumatic fever This was followed by acute pain and swelling of the right ankle and the final illness for which he was admitted to the hospital This diagnosis would provide a logical explanation for both pulmonary and myocardial involvement

In *acute rheumatic fever* sudden pulmonary consolidation may occur as frequently in the upper as in the lower lobes There may be frothy blood tinged sputum with progressive involvement of the lungs and a picture resembling pulmonary edema ending in death in a few hours The pulse rate is rapid and a leukocytosis is present as here

Bronchopneumonia due to the beta hemolytic streptococcus is not rare as a complication in rheumatic fever It seems unlikely that it would have been as fulminating as in this case without more systemic evidence of an acute infection and without bacteremia

Acute rheumatic carditis is usually a pancarditis with involvement of the peri myo and endocardium In this case no pericardial friction rub was heard The evidence of cardiac failure and the gallop rhythm without pre existing hypertension are in support of myocardial disease There was a systolic murmur which according to all observers came late in systole This is almost always indicative of organic mitral insufficiency rather than a functional murmur

The anemia was not great but taken together with the fever and cardiac murmur it raises the question of bacterial endocarditis The blood culture was sterile and there was no evidence of embolism This disease alone would not be expected to produce this fulminating process

Postulating an old and fresh rheumatic myocarditis one must consider the additional possibility of a pulmonary infarct However extensive consolidation would be unusual in such a process at this early stage so one would favor the diagnosis of

Acute rheumatic fever with acute myocarditis and cardiac failure and rheumatic pneumonia

ANATOMICAL DIAGNOSIS (Autopsy No 19390) Ulcerative purulent tonsillitis Acute rheumatic endocarditis (left auricle and mitral valve) rheumatic myocarditis and small infarct like necroses rheumatic pneumonitis Acute phlebitis of efferent veins of liver Acute nephritis Acute splenic tumor with necrosis in Malpighian bodies Pleural effusion Pulmonary edema Cardiac dilatation Obesity (Frohlich type) Hypoplasia of undescended testis

The heart was a little dilated The valves all looked normal except the mitral which was slightly thickened and showed along the line of clo ure a continuous row of rheumatic vegetations The lungs were firm and rubbery and there were many rusty colored hemorrhages on the pleural surfaces The lungs had a uniform reddish brown color and were edematous

The heart lesions were typical especially the fresh lesion in the endocardium of the left auricle the mitral valvulitis and the Aschoff bodies and diffuse cellular infiltration in the myocardium There were also queer focal myocardial lesions with areas of necrosis and infiltrating polymorphonuclear and mononuclear cells suggesting small infarcts No vascular lesions were found to explain the pathogenesis of these areas There was some pulmonary edema and small patches of alveolar hyaline necroses with infiltrating polymorphonuclear cells typical of so called hypersensitive pneumonitis The kidneys showed an early cellular glomerulitis The glomeruli were avascular and contained many intercapillary polymorphonuclear cells Permission for examination of head was not granted

SUMMARY This 15 year old schoolboy with Fröhlich s syndrome had a polyarthritis following measles at age 6 One month before entry he had an eruption thought to be due to scarlet fever recovered uneventfully and then ten days before admission developed a rapidly progressive illness with sore throat cough ankle swelling and dyspnea On admission he was found to have fever tachycardia and respiratory difficulty There was an exudative pharyngitis signs of pneumonitis a presystolic gallop rhythm an apical systolic murmur hepatomegaly and minimal peripheral edema He remained apprehensive became progressively more cyanotic and in spite of penicillin administration the pulmonary signs increased presenting the picture of pneumonitis and pulmonary edema Laboratory examinations revealed some anemia elevated sedimentation rate and leukocytosis Beta hemolytic streptococci were cultured from the pharynx

It seemed evident that the pulmonary manifestations were not due to a simple pneumonitis but were only one event in a rapidly progressive illness with evidence of heart failure due to myocardial involvement In view of the past history of rheumatic fever the preceding streptococcal infection the evidence of arthritis the type of cardiac involvement the anemia and the leukocytosis a diagnosis of acute RHEUMATIC FEVER WITH ACUTE MYOCARDITIS and rheumatic pneumonia was made This was substantiated by the autopsy findings

VII

(#444860 Admitted December 5 1947 Died December 6 1947)

THIS was the fifth admission of this 50 year old Negro laborer a known diabetic who was brought in unconscious In 1934 he was admitted for the first time in diabetic coma with questionable lobular pneumonia The following three admissions in 1935 and 1936 were all necessitated by acidosis resulting from failure to take insulin In 1934 he had a transitory hemiplegia during an insulin reaction It was stated that he was a mild diabetic and only small amounts of insulin were required to lower his blood sugar during acidosis

Ten days before the final admission he developed a shaking chill followed by headache His local physician diagnosed pneumonia and placed him on a sulfonamide Six days before admission he developed headache and some stiffness of the neck He was feverish lost his appetite and three days later had a temperature of 101 He continued to take insulin but ate poorly Two days before admission he was given an additional 40 units of protamine zinc insulin Further insulin was given on December 4 Following the last dose he began to perspire freely respirations increased in rate and he became extremely restless After this he grew progressively drowsy and became disoriented and finally completely unresponsive

PHYSICAL EXAMINATION on admission T 98 P 100 R 32 B P 90/80

The patient was comatose with cold clammy skin and Cheyne Stokes respirations The extremities were very spastic and extended Neck was supple The pupils were small and reacted to light The heart was slightly enlarged to percussion the sounds were of fairly good quality the rate was rapid the rhythm was regular There were a few sticky rales at both lung bases The abdomen was held very tensely and the liver edge extended 2 fingerbreadths below the costal margin

COURSE IN THE HOSPITAL The patient responded immediately to the administration of glucose intravenously The rigidity of his extremities disappeared and respirations reverted to normal rhythm The skin became warm and he regained consciousness but remained disoriented The blood pressure was 125/70 Neck veins were distended Cardiac rate was rapid There was no significant cardiac enlargement and no definite murmur was heard Evidence of pulmonary edema was noted as well as the rales previously described Abdominal wall in the upper portion remained rigid Neurological examination was within normal limits It was thought that he was probably still in mild hypoglycemia because of the large doses of

protamine zinc insulin and that his abdominal symptoms might be related to some cardiac insufficiency He was given digitoxin and further treatment with intravenous glucose The moist rales disappeared but signs in both sides of the chest suggestive of lobular pneumonia persisted He became more and more disoriented The respirations grew rapid and shallow with expiratory grunting A short while later his respirations ceased

LABORATORY DATA Blood serologic test for syphilis negative Red blood count 4 5 million hemoglobin 14 5 gm sedimentation rate 32 mm per hour Leukocyte count was 8 100 on admission but rose to 17 000 before death with predominance of polymorphonuclear cells Urine examination was negative except for clumps of white blood cells and moderately large amounts of sugar Sulfadiazine level on admission was 4 8 mg % Blood chemical studies showed nonprotein nitrogen 73 mg % sugar on admission was 26 mg % rising before death to 328, chlorides 95 mEq CO_2 combining power 25 4 mEq Electrocardiogram showed a sinus tachycardia with a rate of 136 There was a deep S1 T wave was inverted in lead 1 and in chest leads 1 and 5

DISCUSSION This diabetic patient had at least two previous hospital admissions for acute pulmonary infections The story of sudden onset of a febrile illness with a shaking chill followed by the development of signs at the bases of both lungs suggests that he had bilateral lobular pneumonia There is little evidence to support the view that a chronic pulmonary disease such as bronchiectasis formed the background for repeated attacks of lower lobe pneumonitis One has to bear in mind that diabetic patients may suddenly develop active pulmonary tuberculosis but the onset with chill and the localization of the signs in both lower lobes are points against this possibility

This patient had relatively mild diabetes and required little insulin to lower his blood glucose during bouts of acidosis His local physician appreciated the danger of acidosis in the presence of a probable infection but the therapy was too vigorous and the patient entered the hospital in hypoglycemic shock with low blood pressure and narrow pulse pressure and with generalized spasticity It should be emphasized that *hypoglycemia* may give rise to symptoms of nervous system dysfunction This reflects the fact that glucose is the main source of energy for the central nervous system Its oxidation is an integral part of the biochemical process which supplies oxygen for the highly specialized brain tissue hence the effects of severe and prolonged hypoglycemia may be similar to those of anoxia If actual tissue damage occurs symptoms may persist long after the blood sugar level has returned to normal and may be irreversible

Diabetics of the age of this patient are very likely to have arteriosclerosis, often in the cerebral and coronary vessels The resulting

reduction in the blood supply to the brain or heart may cause no symptoms under ordinary circumstances but when the anoxic effects of a severe and prolonged hypoglycemic reaction are superimposed then local tissue damage may result It is an important clinical fact that in elderly diabetics an *insulin reaction* is likely to precipitate a cerebral vascular accident or myocardial infarction The latter event may well have occurred in this patient since cardiac insufficiency de veloped without prior evidence of cardiac disease The sudden death might then have been the result of (1) a cerebral embolus from a mural thrombus, (2) rupture of the ventricle, or (3) development of a fatal arrhythmia such as ventricular fibrillation If there was pre existing coronary atherosclerosis infarction of an extensive degree may have developed during severe hypoglycemia without total occlu sion of the vessel by a thrombus

There is at least one other possible cause of this patient s sudden death—*potassium deficiency* Diabetics with an infection who have been poorly regulated and are approaching acidosis lose large amounts of potassium Moreover the administration of glucose in sulin and epinephrine is followed by a depression of serum potas sium In diabetic acidosis sudden death may result from hypokalemia It is also of some interest that lowering of serum potassium during insulin shock by its depressant effect on neuromuscular activity may mask the typical effects of hypoglycemia Rather striking changes in the S T segments and T waves appear in the electrocardiogram with hypokalemia No such changes were evident here and it seems un likely that potassium deficiency was the cause of the sudden exitus

Extremely sudden death as occurred here is in almost every instance due to some disorder of the circulatory apparatus The three types which one must consider are (1) sudden stopping of the heart ven tricular fibrillation (2) hemorrhage and (3) arterial embolism or thrombosis

For the reasons outlined it seems most probable that this patient had a myocardial infarction

ANATOMICAL DIAGNOSIS (Autopsy No 20953) Hypersensitive reac tion to sulfonamide (?) Diffuse myocarditis with eosinophils Focal necrotizing inflammatory lesions in kidneys Diffuse acute pancreatitis with eosinophils Acute splenic tumor with eosinophils History of diabetes mellitus with recent hypoglycemic reaction Arteriosclerosis of aorta and coronary arteries Organizing thrombosis of left anterior descending coronary artery Organized infarct of apex of left ventricle Fresh mural thrombus in left ventricle Focal fresh myocardial infarcts Recent infarct

of kidney Pulmonary edema Bilateral hydrothorax Embolus in small pulmonary artery Recent pulmonary infarct Mild generalized arteriolo sclerosis

The heart weighed 390 gm All the coronaries were markedly sclerosed and the lumina greatly encroached upon A large branch of the left descending coronary was almost completely occluded and contained numerous arteriosclerotic plaques At the apex of the heart the muscle was greatly thinned out and showed some translucent areas of scarring

Microscopically there was a myocarditis pancreatitis and focal lesions of the kidneys strongly reminiscent of the lesions seen in cases of hyper sensitive reaction to sulfathiazole with periarteritis nodosa The conspicuous eosinophilia in the myocardial pancreatic and splenic cellular infiltrations was noteworthy Arteriosclerosis in the heart was out of proportion to that in the other organs The coronary thrombus and the apical myocardial infarct each appeared several weeks old Pulmonary edema and hydrothorax were considered to be evidences of cardiac failure The heart showed areas of mononuclear infiltration in the myocardium There was also scarring of the left ventricle with diffuse round cell and polymorphonuclear infiltration about the scars An interstitial myocarditis existed There were also multiple new infarcts and a large mural thrombus The left coronary artery was completely occluded by a fresh thrombus

SUMMARY This 50 year old diabetic had had a transient hemiplegia during hypoglycemia in the past Ten days before death he developed a pulmonary infection and was treated with a sulfonamide Two days before admission he was still febrile and was given a large dose of protamine zinc insulin which precipitated hypoglycemic coma After the administration of glucose he improved but signs of cardiac insufficiency became evident The relationship of hypoglycemic reactions to the development of vascular episodes in the diabetic patient was discussed

Autopsy revealed coronary arteriosclerosis with an old thrombus and apical infarct In addition there was a SULFONAMIDE REACTION WITH FOCAL MYOCARDITIS and a fresh coronary thrombus with widespread MYOCARDIAL INFARCTION

VIII

(#1875/1 First Admission November 15 1939 to November 30 1939
Final Admission December 2 1939 Died December 2 1939)

THIS 67 year old broker complained of shortness of breath and dizziness of three months duration One brother died at age 60 of arteriosclerosis and another at age 47 of rheumatic heart disease The patient had inflammatory rheumatism at age 27 with a migratory arthritis lasting for three months

In May 1939 while trying to calm a horse he had a dizzy spell which lasted several minutes After this he had numerous such spells of short duration most of which occurred in relation to exertion He noticed increasing dyspnea on exercise and an occasional feeling of substernal oppression particularly after exertion In 1937 his systolic blood pressure had been recorded at 140 After May 1939 it varied between 102 and 130

PHYSICAL EXAMINATION on admission T P R normal B P 130/86

The patient was lying comfortably in bed Arcus senilis was noted Pupillary reactions were normal The retinal vessels were tortuous and narrow The tongue was slightly red There was dullness to percussion with partial suppression of breath sounds and tactile fremitus at the right base No adventitious sounds were heard The heart was slightly enlarged the left border of dullness extending 11 cm in the 5th interspace and the right 4 cm in the 4th interspace No cardiac impulse was visible or palpable The rhythm was regular The first sound at the apex was poor in quality There was a high pitched systolic murmur at the apex The aortic second sound was louder than the pulmonic second sound The pulses were equal and synchronous The radial vessels were thickened and tortuous The liver and spleen could not be palpated There was moderate clubbing of the fingers sacral edema was noted The dorsalis pedis pulsations were palpable The prostate was slightly enlarged The neurological examination was normal

COURSE IN THE HOSPITAL The patient was placed on digitalis and developed some nausea and anorexia The dose was reduced but these symptoms persisted and the digitalis was discontinued A mild diuresis followed each of three injections of a mercurial The right pleural cavity was tapped and on two occasions a total of 900 ml of a transudate was withdrawn The blood nonprotein nitrogen rose from 34 to 64 mg % At rest in bed the blood pressure fell to 100/60

LABORATORY DATA Blood serologic test for syphilis was negative Hematocrit was 37 8 Leukocyte count 6 400 with 69% polymorphonuclear cells Urine examination showed a specific gravity of 1 012 albumin 1 plus Microscopic examination revealed a rare red cell and 4 to 5 white cells per high power field Blood cholesterol was 259 mg % Venous pressure was 16 cm of water Phenolsulfonphthalein test of renal function showed 65% excretion in 2 hours X ray of the chest on November 16 showed an enlarged left ventricle Aorta was normal in size and shape A pleural effusion was noted at the right base The lungs were described as clear Electrocardiogram on November 16 showed normal sinus rhythm T1 was isoelectric T2 and T3 were upright There was low voltage of the QRS complex in all leads A first degree heart block was present with a P/R interval of 0 23 sec The record was interpreted as indicative of myocardial damage

SUBSEQUENT COURSE After discharge dyspnea was persistent and the patient continued to complain of dizziness On December 2 he collapsed and was unconscious for a period of several minutes There was marked nausea with vomiting but no localized pain The patient was again hospitalized

PHYSICAL EXAMINATION on re admission T 95 P 60 B P 98/80

The patient was cyanotic and respirations were Cheyne Stokes He became progressively more cyanotic and died within a few minutes after admission An electrocardiogram was obtained which showed the rhythm to be grossly irregular with a ventricular rate varying from 30 up to well over 100 No two complexes had the same appearance and they were arising from different foci in the ventricle

DISCUSSION One must decide what led to the development of heart failure and also what event was responsible for the acute sudden episode which was quickly followed by death

It seems likely that some type of myocardial disease was present No valvular lesions were noted There was no history of systemic hypertension and none of the cardinal signs of pulmonary hypertension were present No evidence of pericardial disease or of a congenital malformation was elicited Thus one is left with some myocardial disturbance as the only feasible explanation The facts support this conclusion the heart sounds were of poor quality the blood pressure was low with a rather narrow pulse pressure and no precordial impulse was visible or palpable Furthermore, the electrocardiographic findings supported this diagnosis In the absence of any evidence of syphilis and in the presence of arteriosclerotic changes in the peripheral and retinal vessels, it seems reasonable to assume that the cardiac disease resulted from arteriosclerosis of the coronary vessels The clinical course of the illness prior to the patient s admission to the hospital is consistent with this view The low blood pressure is

suggestive of primary amyloid disease, which may involve the myocardium extensively as well as the muscular coat of the smaller arteries However, there were no associated manifestations to suggest the presence of this obscure and rare disease While in the hospital the degree of cardiac insufficiency increased, and this combined with prostatic hypertrophy may have accounted for the urinary tract infection and rise in blood nonprotein nitrogen

Of interest in this case is the cause of the sudden collapse and death In those cases in which there is sudden stopping of the heart in a person previously in good health one may find no very close correlation between the degree of myocardial damage and sudden death The one mechanism which has been demonstrated under these circumstances although conclusively in only a few cases is the sudden onset of ventricular fibrillation In this case where there is knowledge of pre existing disease and a diagnosis of coronary arteriosclerosis there is a possibility of ventricular fibrillation either with or without myocardial infarction

There is no evidence here of death from loss of blood as from rupture of a dissecting or a ventricular aneurysm The patient undoubtedly had cerebral arteriosclerosis but there is nothing indicative of cerebral hemorrhage

A pulmonary embolus if large, may certainly cause sudden death In this case an embolus might have arisen from either a cardiac mural thrombus or a peripheral vein Rarely are mural thrombi the cause of suddenly fatal pulmonary embolism however emboli originating from the left side of the heart may enter the coronary or cerebral arteries and cause sudden death

It seems most likely on review of these possibilities that what took place was one of the following (listed in order of probability)

(1) Coronary thrombosis or coronary embolism
(2) Coronary insufficiency with ventricular fibrillation
(3) Pulmonary embolism

It is important to remember that the classic symptoms of coronary occlusion may not appear if the patient is already in heart failure There may be simply a sudden increase in cyanosis or dyspnea without characteristic pain In the present case there was no pain but the patient did exhibit shock with prostration sweating nausea and vomiting and fall in blood pressure These are all frequently observed with either coronary occlusion or a large pulmonary embolus and differentiation is extremely difficult Most important in weighing the evidence in favor of a coronary accident here are the knowledge

of pre existing cardiac disease and the type of change seen in the electrocardiogram taken just before death

ANATOMICAL DIAGNOSIS (Autopsy No 16691) Amyloidosis of heart spleen liver kidneys adrenals pancreas parathyroids and arteries Moderate generalized and coronary arteriosclerosis Cardiac hypertrophy and dilatation Hemorrhage into myocardium right auricle Hemorrhage into atheromatous plaque left anterior descending coronary artery Hydro thorax right Passive congestion lungs liver and spleen

The heart was enlarged weighing 570 gm The wall cut with a gritty feeling All the chambers were hypertrophied The liver was symmetrically enlarged weighing 1900 gm It was firm and the margins were sharp and maintained their shape The spleen was symmetrically enlarged

On microscopic examination the heart showed deposits of a pink staining hyaline material sometimes between muscle fibers and sometimes appar ently replacing muscle fibers The branches of the coronary arteries in the heart muscle showed replacement of their walls by this same material Congo red stains made it clear that the material was amyloid and the same substance was present in the adrenals in the Malpighian bodies of the spleen and in the arteries throughout the viscera In the kidneys the walls of the arteries were replaced by amyloid in many places but the glomeruli were not involved There was no indication of the cause of the amyloid deposits The liver showed atrophy and fresh necrosis of cells in the centers of the lobules—the result of chronic passive congestion There were very slight deposits of amyloid

SUMMARY This 67 year old white man complained of dyspnea and substernal oppression with dizzy spells on exertion for 6 months before death Physical examination revealed peripheral and retinal arteriosclerosis The heart was enlarged the sounds were of poor quality and an apical systolic bruit was described Evidences of cardiac insufficiency were present and the electrocardiogram revealed changes indicative of myocardial damage Blood pressure at rest in bed was 100/60 A sudden attack of nausea and vomiting occurred with circulatory collapse and death The clinical picture suggested heart failure due primarily to myocardial disease with the most likely cause coronary arteriosclerosis Autopsy revealed AMYLOIDOSIS WITH INFILTRATION OF THE MYOCARDIUM The muscula ture of the visceral arterioles was replaced by the amyloid which may have accounted for the rather low blood pressure

IX

(#200678 First Admission June 3 1940 to August 12 1940
Second Admission January 14 1942 to February 23 1942
Final Admission January 12 1943 Died January 20 1943)

THIS 23 year old Negro was under observation for a period of three years

The present illness began about March 1940 with easy fatigability In the ensuing three months the patient lost 30 lb in weight He began to have dyspnea on mild exertion which grew progressively worse and was soon accompanied by edema of his ankles In May 1940 a pleuritic type pain developed in the right side of the chest His symptoms gradually grew worse and he was admitted to the hospital

PHYSICAL EXAMINATION on first admission At this time the patient was acutely and chronically ill underdeveloped and quite emaciated There was marked dyspnea and orthopnea Moderate generalized lymph node enlargement was noted There was venous distention on the left side of the neck The trachea was deviated to the right Dullness and suppression of the breath sounds were noted over the right hemithorax as well as over numerous areas in the left hemithorax The heart was normal in size sounds were of good quality and no murmurs were heard It was noted that he had a paradoxical pulse The liver extended 4 fingerbreadths below the costal margin A nodular mass which was believed to be omentum was felt in the epigastrium There was pitting edema of both legs

LABORATORY DATA Hemoglobin was normal Leukocyte count was 5 000 Urine contained 3 plus albumin and 4 plus urobilin Wassermann was negative and sputum examination did not reveal any tubercle bacilli Total serum protein was 6 35 gm with 2 99 gm of albumin Tuberculin test was negative Venous pressure on admission was 370 and on discharge 150 mm of water X ray examination showed marked shift of the trachea to the right with infiltration of the left upper lobe and throughout the entire right side of the chest The diaphragm was slightly elevated on the right The heart was not displaced or enlarged

COURSE on first admission The patient was digitalized given diuretics and rapidly improved A tachycardia was present at the time of discharge and he ran a low grade fever for seven weeks

Following discharge he was able to perform light duties as a chauffeur At the end of a year dyspnea increased he became orthopneic and again noted ankle edema He was readmitted in January 1942

PHYSICAL EXAMINATION on second admission T 100 P 110 R 50 B P 110/100

There was marked dyspnea and orthopnea Slight cyanosis was evident and the cervical veins were prominent All four extremities and the back were markedly edematous and there was pitting edema over the chest There was no lymph node enlargement The chest moved little on inspiration There was marked asymmetry of the two sides the left being much deeper and better developed than the right which was quite flat There was dullness at the left lung base and many fine rales were heard extending into the left axilla A questionable area of egophony was heard over the left lower lobe The right hemithorax was dull particularly in the right axilla and toward the base The breath sounds were blowing in quality over the right side of the chest and had a definite cavernous quality Over the lower half the sounds were suppressed Numerous rales were heard throughout The radial pulses were extremely rapid but were regular and of small volume The heart was tremendously enlarged and globular in shape A definite apical impulse was felt in the midaxillary line The sounds were loud but the quality was poor There was a loud systolic murmur at the apex The venous pressure was elevated

COURSE on second admission Pericardial tap was done and 250 ml of straw colored fluid containing numerous lymphocytes was removed followed by relief of symptoms No tubercle bacilli were found in the fluid Tuberculin tests were negative The patient s course was uneventful after the tap The temperature remained elevated for 10 days and there was a tachycardia The pulmonary signs improved greatly and the edema cleared Bromsulfalein test showed 20% retention after 30 minutes Total serum protein 8 34 gm % with 3 89 gm % of albumin Serum calcium was 10 2 mg % phosphorus 4 3 mg % and phosphatase activity normal X ray of the chest showed marked fibrosis of the right lung base with some thickening of the pleura The trachea and mediastinum were displaced to the right and there was slight diffuse fibrosis of the left lung The heart was found to be enlarged in all diameters Electrocardiogram showed numerous premature auricular beats The P R interval was prolonged (0 23 sec)

After discharge the patient was fairly well until early 1943 when increasing dyspnea cough weakness and peripheral edema again necessitated hospitalization

PHYSICAL EXAMINATION on third admission The patient was found to be chronically ill in a very poor state of nourishment quite dyspneic and orthopneic Trachea was again deviated to the right and the jugular veins on the left were greatly distended The chest was asymmetrical as previously noted and there was a precordial bulge There was dullness over the entire right side of the chest with increased tactile fremitus anteriorly and over the upper half posteriorly Over this area there was tubular breathing Numerous coarse crackling rales were heard The heart was enlarged to the left The point of maximal impulse was 13 cm in the 5th interspace Rhythm was regular and rapid There was a rough apical systolic murmur and also a systolic bruit over the base Blood pressure was 130/110 There was a marked pulsus paradoxus The liver was felt 3 fingerbreadths below the costal margin Axillary hair was noted to be scant and the patient appeared to be 14 or 15 rather than his actual age of 23

Venous pressure was again found to be high (250 mm of saline) On rest in bed and further digitalization the edema disappeared However the pa tient s general condition did not improve and on January 20 his respirations became irregular and the pulse imperceptible The temperature began to rise and the patient died a few hours later

DISCUSSION This patient presented numerous clinical findings during the three years preceding his death It might be well to reca pitulate the major features in chronological order so as to have a clear conception of the manifestations for which the diagnosis must furnish a satisfactory explanation

(1) The total duration of illness was three years with a relapsing course

(2) There was involvement of the lymphatic system as evidenced by the general lymph node enlargement

(3) On each examination there was pulmonary infiltration and fibrosis which was asymmetrical in distribution These changes were not due solely to chronic passive congestion as evidenced by the small volume of the right hemithorax and the shift of the trachea

(4) From the first examination evidence was presented of cardiac insufficiency with venous distention enlargement of the liver and edema which improved rapidly after the administration of digitalis On the second admission the heart was greatly enlarged to both right and left, and a loud systolic murmur was audible Fluid was removed from the pericardium Later the patient had a low pulse pressure high venous pressure persistent paradoxical pulse, and cardiac en largement without evidence of a large effusion into the pericardial sac The electrocardiograms showed first degree heart block and numerous auricular premature beats

The sequence of events is not typical of pericarditis with scar for mation leading to the development of the syndrome of inflow stasis (constrictive pericarditis) Nevertheless the patient seems clearly to have had pericardial involvement with development of an effusion on at least one occasion The first episode of failure with improve ment after digitalis and the later development of marked cardiac enlargement low pulse pressure and extensive edema suggest that there may also have been myocarditis If any significance may be ascribed to the murmurs which developed there may have been endo carditis as well

In view of the multiplicity of the lesions and the chronicity of the illness three main possibilities must be considered (1) a lymphoma of some type (2) tuberculosis and (3) sarcoidosis Consideration



must also be given to the possible simultaneous occurrence of tuber culosis and sarcoidosis There is nothing to support a diagnosis of syphilis and the duration the relapsing course and the distribution of lesions rule out a malignant neoplasm

Hodgkin s disease or lymphosarcoma with predominant involve ment of the lungs and heart leading to cardiac insufficiency would be most unusual On the basis of these diagnoses it would also be diffi cult to explain the spontaneous disappearance of the general lymph node enlargement

There are numerous features of the clinical picture in this case which lead one toward a diagnosis of tuberculosis Lymph node involvement is not too unusual in tuberculosis and the chronic ill ness with extensive involvement of the lungs and features suggestive of a constrictive pericarditis is quite consistent with this diagnosis This disease is common in Negroes and may run a course of fluctu ating severity The signs suggestive of cavitation in the right upper lung also point in the same direction However when one probes a little deeper into the facts certain considerations arise which cast doubt upon a diagnosis of tuberculosis It seems difficult to explain on this basis the fairly long partial remission which the patient enjoyed particularly since he was a young Negro with acute and ex tensive involvement of the lungs Furthermore tuberculosis does not provide a wholly satisfactory explanation of the cardiac findings Still further if tuberculosis were responsible for such widespread pul monary lesions with concomitant enlargement of lymph nodes and progressive involvement of the heart one would have expected some positive results either from the numerous examinations for tubercle bacilli or from the tuberculin tests The sequence (1) heart failure with a relatively small heart (2) pericardial effusion (3) constrictive pericarditis (4) cardiac enlargement would be an unusual sequence for tuberculosis of the pericardium As mentioned earlier the events suggest myocardial involvement as well Tuberculous lesions in the myocardium extensive enough to impair function are extraordinarily rare

On the other hand none of these events is difficult to explain if the patient had *sarcoidosis* This disease may affect any organ or tissue in the body and for this reason it appears in a great variety of clinical forms The numerous descriptions of this disease devote much atten tion to the changes in the lungs lymph nodes skin and bones as well as in the structures of the eye and various portions of the nervous system Since the original report of Salvesen in 1935 of a patient with

sarcoid who had bundle branch block evidence has accumulated that the myocardium and pericardium may be the seat of sarcoid lesions in a relatively large number of cases Such lesions occurred in 4 of 21 recorded autopsies in one series and at least 3 of these patients had symptoms of myocardial failure during life Cardiac enlargement was present in most cases and a low pulse pressure was recorded Cardiac arrhythmias or disturbances in conduction were fairly consistently recorded Thus this disease will explain the chronic relapsing course the presence and disappearance of the lymph node enlargement—since spontaneous healing is common in sarcoidosis the lung findings and finally the involvement of the heart which probably was responsible for the fatal outcome

ANATOMICAL DIAGNOSIS (Autopsy No *18196*) Sarcoid involving lungs pleurae heart pericardium lymph nodes liver spleen vertebrae femur marrow Schaumann bodies in lung and pleura Obliteration of right pleural cavity by dense scar Primary tuberculous complex right lung Atelectasis right middle and lower lobes Stenosis right upper lobe bronchi with bronchiectatic cavity formation and scarring Constriction of great vessels at base of heart by scar Cardiac dilatation with right ventricular hypertrophy Chronic passive congestion of liver and lungs Hydrothorax left Dilatation of left internal jugular vein

The epicardial surface of the heart was diffusely thickened and opaque *Both sides of the heart showed rather marked dilatation and the walls of* the right auricle and ventricle looked hypertrophied Valves were competent and delicate At the apex of the left ventricle in a localized area the endocardium was thickened and in this region there were some gray scars in the myocardium The left lung showed patchy thickening of the pleura everywhere The right lung was small and almost completely encased in a very thick cartilaginous pleura The upper half was mostly occupied by a cavity with relatively smooth lining Its outer walls seemed composed almost entirely of thickened pleura The large bronchus leading toward this was obstructed The pericardial sac showed rather marked thickening and scarring

Sections of the lungs showed scattered hard tubercles of epithelioid and giant cells in the central portion with epithelioid cells and lymphocytes at the periphery Characteristic Schaumann bodies were seen Section of the right lung showed considerable scarring about a large bronchus with well developed bronchiectasis The pericardium overlying the left ventricle was thickened with scarring which dipped down for a short distance In the interstitial tissue of the myocardium foci of hard tubercles made up of epithelioid and giant cells were noted

SUMMARY *This 23 year old* Negro chauffeur had a relapsing disease of three years duration characterized by pulmonary infiltration lymph node enlargement and cardiac insufficiency with venous hypertension hepatomegaly and edema Early in the course the heart was not signifi

cantly enlarged later a pericardial effusion developed and finally there was persistent increase in the area of the cardiac shadow The findings suggested myocardial as well as pericardial involvement and three main causes were considered lymphoma tuberculosis and sarcoidosis Autopsy revealed extensive SARCOIDOSIS There were scars partially constricting the vessels at the base of the heart scarring and fresh sarcoid tubercles were found in the pericardium and myocardium There were sarcoid nodules in the lungs but the major change was the result of peribronchial scarring with bronchial compression and bronchiectasis

X

(#535946 Admitted April 27 1950 Died April 28, 1950)

This 38 year old housewife entered from another hospital with a diagnosis of collagen vascular disease type undetermined

She had had scarlet fever at age 14 and a tonsillectomy and adenoidectomy at age 8 Her general health was excellent until the onset of the present illness

In 1948 she complained of pruritus of the feet No cause could be found for the difficulty She had episodes of crying and became irritable During these periods her heart pounded and was rapid but there was no irregularity *She began to complain that going up steps took everything* out of her, seemingly this was due to general weakness and not to dyspnea At night the husband noted that her heart was fast and active On a few occasions she complained of some vague abdominal distress There was never any evidence of arthritis or involvement of serous membranes In December 1949 she gave birth to a normal child her second At no time during any of the examinations was attention called to any cardiovascular disease Following delivery her condition did not change until March 1950 when shortness of breath was noted After one week she consulted a physician who made a diagnosis of heart failure For the first time a murmur was noted at the apex and evidences of congestive heart failure were described Enlargement of the liver was noted The patient was given digitalis but the liver did not decrease appreciably in size This suggested the possibility of constrictive pericarditis but x ray and fluoroscopic studies seemed to rule out this possibility By March 15 her only complaint was slight dyspnea About April 1 she developed thickness of speech and weakness and numbness of the left side of the face and the left hand On questioning she recalled three similar episodes *in the previous two years* They were transient without residual impairment of function During this period she lost weight gradually

Physical Examination on admission T 96 4 P 98 R 26 B P 90/80

The patient was extremely ill and semicomatose There was loss of weight and the mucous membranes appeared pale The tips of her fingers and toes were very blue She seemed to be reasonably comfortable lying flat in bed and was not obviously orthopneic There was slight sacral edema The neck veins were distended The radial pulses were regular but of small volume Pupils reacted normally to light The discs were well outlined There were no vascular abnormalities No exudates hemor

rhages or cytoid bodies were noted in the retinas The chest was resonant The lung fields were remarkably clear with only a few moist rales at each base The precordium was active with easily visible pulsations There was a questionable systolic thrill at the apex. The cardiac dullness seemed to extend further to the left than the visible apical impulse suggesting the possibility of a pericardial effusion There was an unusually loud harsh coarse systolic murmur maximum in intensity at the apex which was transmitted over the entire precordium and into the axilla and was audible over the left posterior chest There was no definite diastolic murmur The apical first sound was loud A sharp liver edge was felt well below the umbilicus There was a greatly enlarged spleen There was no edema The dorsalis pedis pulsations could not be felt

COURSE IN THE HOSPITAL The cyanosis improved with oxygen administration and the pulse seemed stronger The next morning there was extreme dyspnea and numerous moist rales were heard at both lung bases The pulse was almost unobtainable and very rapid Blood sugar examination showed hypoglycemia Following administration of 50 cc of 50% glucose the patient improved transiently but then rapidly failed and died within 24 hours of admission to the hospital

LABORATORY DATA Serologic test for syphilis negative Hematocrit 42 2 sedimentation rate 0 mm per hour smear normal Leukocytes 16 850 with 28% juvenile neutrophils 63% segmented neutrophils 2% eosinophils 3% lymphocytes 4% monocytes Urine specific gravity 1 016 with a few granular casts Blood nonprotein nitrogen 48 mg % blood sugar 23 mg % several blood cultures were sterile

Electrocardiogram showed sinus tachycardia and changes indicative of right ventricular strain X ray of chest showed generalized enlargement of the heart with an inconspicuous aorta The configuration was compatible with enlargement of the right and left ventricles with a double valve lesion The hilar shadows and lung markings were however not accentuated to any extent although there was evidence of minimal interstitial fibrosis in both lung fields which might be secondary to passive pulmonary stasis chronic in type

DISCUSSION The central feature of this case was heart failure of fairly sudden onset progressing without definite response to treatment at any stage, to death within a total period of about 3 months There were certain unusual features which seem to narrow the diagnostic possibilities to three or four

(1) In spite of numerous examinations both before and during pregnancy no cardiac murmur was ever described until an examination in March 1950

(2) The illness was never accompanied by any fever

(3) Terminally in the presence of congestive heart failure there was evidence of forward heart failure as well

(4) Once the liver became enlarged it never regressed in size, and
(5) Orthopnea was never a prominent feature

On the evidence one can eliminate any form of congenital heart disease and there was never evidence of hypertension in the systemic circulation The heart was active and not greatly enlarged and the studies done prior to admission seem to rule out primary disease of the pericardium In view of the cardiac size and the absence of any gallop rhythm one would be reasonably certain that disease of the myocardium was not the essential cause of the heart failure The basis for the heart failure must then be either hypertension in the pulmonary circulation or valvular heart disease or perhaps a combination of these two The persistence of the heart failure particularly the continued hepatic enlargement strongly suggested some type of irreversible obstruction to normal blood flow through the heart or lungs It seems obvious from the history that there was no high degree of mitral stenosis shortly before the cardiac insufficiency began and it therefore seems unlikely that mitral stenosis alone without some complicating feature such as active rheumatic carditis could have brought about this fulminating illness In view of these considerations it seems that there are four conditions assuming the heart itself to be the original seat of difficulty which might adequately explain all of the events which took place during the course of this patient s illness

(1) Rheumatic heart disease with mitral involvement and active rheumatic carditis
(2) Chronic rheumatic disease of the mitral valve with superimposed bacterial endocarditis
(3) Multiple pulmonary emboli with chronic cor pulmonale
(4) A rare condition in which the left auricle is filled to the point of obstruction by a myxomatous tumor

Superficially the first diagnosis which would be the most common in occurrence and therefore the most probable would seem to fit the situation However close analysis reveals certain strong points against it *There was no evidence of any active infection during the* patient s illness under long observation The heart shadow was not very greatly enlarged the shape was not typical of mitral stenosis and none of the characteristic features of active myocarditis was present The cardiac impulse was forceful and there was no gallop rhythm It is quite inconceivable that such loud and unequivocal murmurs would have been overlooked during the many examinations the pa

tient had prior to the onset of the acute illness It is even more unlikely that such obvious mitral valvular disease would have de veloped so rapidly in a woman of this age without evidence of active rheumatic fever

The second diagnosis in the list would offer a more plausible explanation for the auscultatory findings A minimal mitral lesion with a very minimal murmur might have been overlooked If there had been bacterial endocardial implants following delivery, as may occasionally happen, then the subsequent vegetative growth might account for a sudden increase in the intensity of the murmurs How ever there are certain rather strong points against this hypothesis (1) The cerebral symptoms appeared before there was any reason to suspect bacterial endocarditis (2) There was never any febrile reac tion although the patient received no antibiotics (3) No embolic phenomena were ever noted and blood cultures showed no growth (4) Such severe and persistent heart failure could hardly be accounted for by bacterial endocarditis with no more than a minimal mitral lesion

There is the possibility, of course that emboli to the lungs from mural thrombi or from vegetations in the right heart chambers or from a peripheral source might have contributed to the sympto matology Obstruction of a major portion of the pulmonary arterial bed by emboli may lead to chronic cor pulmonale with murmurs of the type heard in this case However if emboli came from a periph eral source one would have no explanation for the cerebral episodes occurring before the heart murmur and failure appeared Moreover there were no episodes of acute pain, dyspnea or hemoptysis sug gesting large pulmonary emboli

Myxomatous tumors growing in the left auricle may give rise to intermittent or progressive signs of mitral stenosis coming on rather late in life without previous evidence of rheumatic fever or valvular disease Since the other possible diagnoses do not fit the present situation without the postulation of an unusual course of events myxoma of the left auricle must be considered in spite of its rarity In the early stages friable bits of the myxoma may become free in the blood stream and lead to small cerebral emboli As the tumor grows with obstruction of the entry of blood into the left ventricle heart failure may develop and the auscultatory signs may be sugges tive of mitral stenosis This would adequately explain the appearance of these signs in a patient who repeatedly examined over the previous two years never had any evidence of valvular heart disease As the

size of the tumor increased signs of forward heart failure with small rapid pulse and cold cyanotic extremities would result from the obstruction to the flow of blood through the heart From the evidence it seems reasonable to postulate that this patient had a tumor mass filling the left auricle

ANATOMICAL DIAGNOSIS (Autopsy No 22383) Myxoma of left atrium with tumor emboli to coronary renal and splenic arteries Dilatation of all cardiac chambers Scarring and atrophy of myocardium Serous effusions of thoracic pericardial and abdominal cavities Chronic passive congestion of lungs and viscera with central necrosis of the liver lobules Infarcts kidney History of hemiplegia Duodenal ulcer Adenomata parathyroids *Leiomyomata uterus Excess ground substance aortic media*

The pleural cavities contained more than a liter each of straw colored fluid The heart was firm and weighed 300 gm Opening of the left atrium revealed a mass which completely filled the atrial cavity It was large and irregular and had a villous contour It apparently arose from the endocardium on its septal surface along a transverse 2 cm area just above the foramen ovale and overlying the middle mitral leaflet Both ventricles and the right atrium were dilated The liver was firm and had a nutmeg appearance

Microscopically emboli from this tumor were found in many viscera some quite recent while many were older and organizing The latter had produced infarct like scars in the myocardium and infarcts in the kidneys There was extreme chronic passive congestion in the lungs liver and pancreas The tumor was composed of myxomatous material which revealed metachromasia with toluidine blue stain and interspersed hemorrhages and giant fibrocytes

SUMMARY This 38 year old housewife had vague symptoms with palpitation and fatigue for 2 years Two months before death she developed dyspnea and progressive heart failure She had several episodes of transitory left hemiparesis The heart had been repeatedly examined but no murmur was heard until 2 months before death when a systolic bruit was noted Examination revealed venous hypertension pulmonary edema and hepatomegaly The pulse was rapid and of small volume and the extremities were cold and cyanotic The heart was enlarged and a systolic murmur and thrill were noted over the precordium The fasting blood sugar was 23 mg / Several possibilities were considered as to the cause of the heart disease which had been rapid and progressive It was known that the murmur had only recently appeared and the manifestations suggesting intracardiac obstruction to blood flow led to the diagnosis of MYXOMA OF THE LEFT AURICLE This lesion was found at autopsy and there were numerous tumor emboli of various ages Of interest is the development of hypoglycemia which was assumed to be related to the severe chronic passive congestion of the liver

XI

(#448535 Admitted January 17 1949 Died January 20, 1949)

THIS 53 year old white male entered complaining of dyspnea hemoptysis and severe dysphagia of five days duration He had a penile sore in his youth but received no treatment He was a chronic user of alcohol One year previously he had been admitted with a five month history of edema of the ankles weakness in the legs dyspnea cough hoarseness dysphagia and signs of urinary obstruction There was a pulsating mass over the left upper chest near the sternomanubrial junction over which a rough systolic and a short diastolic murmur were heard Blood pressure was 122/70 There was no evidence of cardiac insufficiency He had hypoactive ankle jerks and diminution of vibratory perception over the lower legs The knee jerks were hyperactive Cystometric studies revealed neurogenic bladder dysfunction Evidence of prostatic hypertrophy was found and a trans urethral resection was done The blood serologic test for syphilis was positive and he received 5 8 million units of penicillin

He continued to complain of exertional dyspnea hoarseness and dysphagia One of the main difficulties was progressive weakness of the legs which made walking and finally even standing difficult Examinations showed venous distention hepatomegaly edema of the ankles and a moderate degree of cyanosis In addition to the previous findings neu rological examination revealed loss of vibratory perception below the waist with hypesthesia and diminished sensation to deep pain below the level of the knees

Five days before final admission the patient noted sudden onset of severe dyspnea and orthopnea with cough productive of blood tinged sputum Orthopnea was severe and he was forced to sit up for the following four nights He noted aching pain at the costal margins associated with respiration and pain in the right upper abdominal quadrant The dyspnea continued and he grew progressively weaker

PHYSICAL EXAMINATION on admission T 99 P 108 R 28 B P 132/58

The patient was in acute di tress due to severe dyspnea and orthopnea Respirations were Cheyne Stokes in character He was apprehensive appeared pale and was sweating profusely There was cyanosis over the lower extremities The legs were swollen mottled in appearance and cold There was clubbing of the fingers He coughed frequently Examination of the fundi showed tortuosity of the vessels The pupils reacted normally The veins in the neck were prominent more so on the right The trachea was deviated to the right and there was a tug There was bulging over the

left upper chest This region lagged on inspiration There was a visible heave with each heart beat and a palpable systolic and diastolic thrill were felt over the left upper chest There was an area of dullness extending to the left 8 5 cm in the 2nd interspace and 14 5 cm in the 5th interspace There were signs of fluid over the right lower chest posteriorly Breath sounds were bronchovesicular throughout with scattered wheezes Medium moist rales were heard at both lung bases A pleural friction rub was heard in the right upper axilla The heart sounds were loud Over the entire precordium there were a harsh diastolic murmur and a very loud systolic murmur both heard most prominently over the pulsating area The aortic second sound was replaced by the diastolic murmur The right radial pulse was stronger than the left The liver edge was 3 fingerbreadths below the costal margin The neurological abnormalities were as previously described

COURSE IN THE HOSPITAL The patient was treated for cardiac insufficiency His condition did not improve however and the dyspnea became progressively more severe He had difficulty in swallowing which precipitated a distressing cough His pulmonary edema increased and he died on the fourth day

LABORATORY DATA Blood serologic test for syphilis positive titer 64 units Hematocrit 44 sedimentation rate 23 mm per hr leukocytes 10 700 with a normal differential count The urine had a specific gravity of 1 024 with a trace of albumin 10 white and 4 red cells per high power field and numerous hyaline and granular casts Blood nonprotein nitrogen was 115 mg % CO_2 17 4 mEq and chloride 91 5 mEq Venous pressure 85 mm glucose Circulation time 36 sec (Decholin) Fifteen hundred ml of slightly blood tinged transudate was removed from the right chest X ray examination of the chest showed a huge aneurysm of the arch and descending portion of the aorta Severe pulmonary congestion with accumulation of fluid in both pleural cavities

DISCUSSION There seems to be no reasonable doubt that this man had syphilis with an aneurysm of the aorta and in all probability meningovascular syphilis as the basis for the neurological abnormalities There was a history of an untreated penile lesion The hoarseness cough dyspnea and dysphagia could all have been associated with compression of various mediastinal structures by an aneurysm This view is strongly supported by the roentgen examinations At the time of the first admission there was no definite evidence of cardiac insufficiency and there were no unequivocal signs of aortic insufficiency The patient received treatment with penicillin and got along reasonably well for a year during which time the objective evidences of cardiovascular and spinal cord disease changed very little

However five days before the final admission the situation changed rather dramatically and he developed severe dyspnea and orthopnea Examination revealed evidence of severe cardiac insufficiency and signs of an aneurysm including a well defined tracheal tug There

were also at this time a prominent systolic and diastolic thrill with accompanying murmurs and a wider pulse pressure than had previously been noted The point of interest is what took place to account for this final acute episode, which led to death in about 9 days The onset of the dyspnea was not associated with any severe pain

The patient might have had a pulmonary embolus There had been chronic difficulty with the lower extremities and an operation on the prostate which might have been followed by phlebothrombosis The pleurisy with effusion might have been secondary to an embolic episode but such an episode could hardly account for the changes in the auscultatory signs Likewise there was little to support the possibility of sudden occlusion of a coronary artery from the point of view of either the symptoms the signs, or the laboratory findings

The sudden onset of such severe dyspnea and the development of a loud systolic and diastolic thrill and murmur in the region of the aneurysm suggest very strongly the development of an abnormal communication between the general circulation and the pulmonic circulation Such a communication may develop between the chambers of the heart or between the aorta and the pulmonary artery Occasionally a systolic murmur and thrill may result from a congenital fibrous band running across the left ventricle but in most instances the sudden development of bizarre auscultatory findings of this type is associated with a shunt between the greater and lesser circulatory systems A classification of the causes of murmurs and thrills of this type is given in Table 5

In the present case the only possibility which might be entertained among the congenital lesions would be patent ductus arteriosus but even here development of the communication so late in life would be unusual and the associated findings suggest more strongly that the cause will be found among the acquired lesions

There was no evidence to suggest the development of bacterial endocarditis and it would be altogether unusual for an interventricular septal defect secondary to septal infarction to result in such striking and severe manifestations and in this location There was, on the other hand a history of syphilis a positive serologic test for syphilis and evidence of an aortic aneurysm and of central nervous system manifestations compatible with a syphilitic etiology The sudden development of severe dyspnea and orthopnea together with the recorded changes in the cardiac manifestations suggests that a communication developed between a syphilitic aneurysm of the aorta and the pulmonary artery

Table 5 Causes of a Systolic Murmur and Thrill in the 2nd 3rd 4th Interspaces (left) (Modified after Hamman)

I Communication between systemic and pulmonic circulations

A Congenital

1 Interventricular septal defect
2 Interauricular septal defect
3 *Patent ductus arteriosus*
4 Perforation at *base of right anterior sinus of Valsalva which* extends into pouch located between wall of aorta and pulmonary conus

B Acquired

1 Rupture of intraventricular septum from softening of a septal infarct
2 Rupture of a mycotic aneurysm at base of aorta into pulmonary artery
3 Rupture of syphilitic aneurysm into pulmonary artery

II Congenital fibrous band traversing the left ventricle

III Ball valve tumor of the auricle (signs may be intermittent and change with position)

A Thrombus

B Myxoma

IV Pulmonic hypertension with chronic cor pulmonale due to repeated pulmonary emboli

Before making this diagnosis *with finality it would be wise to con*sider one other possibility—dissecting aneurysm Although this type of aneurysm is unusual in the presence of syphilitic aortitis such a *diagnosis* might explain many of the findings *including the auscul*tatory phenomena particularly if rupture back into the main aortic stream took place This possibility however is a remote one although the signs of aortic insufficiency not infrequently develop under such circumstances The most likely diagnosis then would seem to be *rupture of an aortic aneurysm into the pulmonary artery* White Chamberlain and Kelson reported 13 such cases from the literature In five the patient survived for two months or longer after onset of symptoms The most conspicuous signs were (1) a continuous murmur in the area of the pulmonary valve (2) bulging of the pulmonary artery in the x ray and (3) rapid appearance of congestive heart failure

ANATOMICAL DIAGNOSIS (Autopsy No 21621) Syphilitic aortitis *with large saccular aneurysm of ascending arch and upper thoracic aorta* Rupture of aneurysm into main pulmonary artery dilatation and hypertrophy of right ventricle of heart Bilateral hydrothorax partial atelectasis and focal emphysema of the lungs Slight meningeal thickening of frontal

parietal lobes of brain and of the spinal cord slight generalized cortical atrophy, varicosities of anterior and posterior spinal vessels focal demyelinization of lateral pyramidal tracts and dorsal columns of cord history of peculiar neurological symptoms and neurogenic bladder chronic cystitis hypertrophy of bladder wall Scarring organizing and fresh pneumonia of lungs Squamous metaplasia of bronchial epithelium upper lobe right lung squamous carcinoma upper lobe right lung Generalized arteriosclerosis

The heart was enlarged with right ventricular hypertrophy and dilatation The superior vena cava was depressed and distorted by a huge anterior mediastinal mass Immediately above the aortic valve ring the aorta was extremely dilated and formed a saccular aneurysm which was about 10 cm in diameter and filled with thrombus material The wall was thin and made up of fibrous tissue lined with scarred intima in which arteriosclerotic plaques were present The saccular aneurysm opened into a greatly dilated descending aorta which for 10 cm was almost filled with a large organizing thrombus

At the bifurcation of the pulmonary artery there was a perforation into the posterior portion of the aneurysm which measured almost a centimeter in diameter The anterior portion of the left lower lobe was the seat of a massive lobular pneumonia

Of interest was the complaint of severe weakness of the legs and the coldness and localized cyanosis of the lower limbs This may have been accounted for by the organizing thrombus filling the aneurysm of the descending aorta

There was clearly considerable pressure of the aneurysm upon the pulmonary artery The heart was dilated between the pulmonary valve and the site of pressure of the aneurysm It is possible that the diastolic murmur was not a murmur of aortic insufficiency but rather was due to dilatation of the pulmonary ring The aortic valve was normal and there were no peripheral signs of aortic insufficiency The right ventricular hypertrophy was doubtless due to the pressure of the aneurysm on the pulmonary artery Some sections of the lung showed a great deal of fresh pneumonia and in other places there was organizing pneumonia

SUMMARY This 53 year old white male had a history of untreated syphilis One year before admission he was found to have a pulsating mass over the left upper chest over which a systolic and a diastolic murmur were heard Eight days before death there was sudden onset of severe dyspnea and orthopnea There were tachycardia Cheyne Stokes respirations cyanosis signs of pulmonary edema and over the left upper chest a visible heave was noted There were systolic and diastolic thrills and murmurs In spite of treatment for cardiac insufficiency the dyspnea which was greatly aggravated by cough became more severe and the pulmonary edema increased The serologic test for syphilis was positive X ray showed a huge aneurysm of the arch and descending portion of the aorta

The sudden onset of cardiac insufficiency and the peculiar systolic and diastolic thrill and murmur suggested the presence of a communication between the systemic and pulmonic circulation After consideration of the

various possible causes it was postulated that a SYPHILITIC ANEURYSM OF THE AORTA HAD RUPTURED INTO THE PULMONARY ARTERY This was the condition found at autopsy

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Chapter 3

PAIN IN THE CHEST

PAIN IN THE CHEST is frequently a presenting complaint Its significance to the patient is usually more ominous than that of other symptoms As a result he goes to his doctor complaining of this particular symptom when it may be only the most recent in a series of events which had previously been ignored Usually the pa tient *suspects that his chest pain is indicative of heart trouble* and frequently the physician s efforts are directed toward confirming or denying this suspicion

Thoracic pain may have its origin in the various tissues of the chest wall the neck the intrathoracic structures or the structures below the diaphragm When the pain arises in the skin or superficial struc tures it can usually be accurately localized by the patient When it arises in deeper structures it may be of a diffuse type which defies accurate localization or it may radiate in such a manner as to mis lead both patient and physician into believing that the cause of the disturbance lies beyond the limits of the thorax The lack of any apparent relation between the location of the pain and the site of the disturbance may be explained by the fact that many thoracic struc tures among them the heart, aorta pleura and esophagus are sup plied by sensory fibers from the same segments of the spinal cord The pain of angina pectoris may be felt along the inner aspect of the left arm owing to the common innervation of the heart and the affected area of the skin by the 8th cervical and 1st thoracic segments

Since there are many causes of chest pain, this symptom frequently serves as a hub about which various diagnostic possibilities may be assembled It is always important to obtain a detailed description of the pain, the circumstances under which it arises and the factors which influence it either favorably or unfavorably A careful history frequently provides crucial information which saves the time and

expense of elaborate diagnostic procedures For example, the pain produced by extrusion of an intervertebral disc in the lower cervical region may closely simulate that of angina pectoris However the similarity vanishes when questioning discloses that the pain is produced not by exertion but rather by movements of the neck and by such acts as coughing and sneezing Many times the facts brought out in the history may be verified or clarified by asking the patient to perform under observation the acts which have been found to precipitate or relieve the pain A meticulous physical examination is just as important as a full and accurate history The discovery of crepitation or localized tenderness at the site of an unsuspected rib fracture may provide a quick and simple explanation for what had appeared to be a complicated problem

The causes of pain in the chest may be classified for practical purposes of differential diagnosis as shown in Table 6

Table 6 Pain in the Chest

I Pain originating in the tissues of the neck or chest wall
- A Skin
- B Muscles
- C Bones and cartilages vertebrae ribs sternum
- D Spinal cord and sensory nerves
- E Blood vessels
- F Mammary glands

II Pain originating in the heart
- A Myocardial ischemia
  - 1 Relative ischemia not attributable to condition of the heart itself due to
    - a Extreme exertion
    - b Thyrotoxicosis
    - c Low diastolic pressure (e g aortic insufficiency)
    - d Severe anemia
  - 2 Absolute ischemia due to partial or complete occlusion of coronary arteries at their mouths or somewhere along their course
    - a Angina pectoris due to partial occlusion of coronary arteries resulting from coronary arteriosclerosis or syphilitic disease involving mouths of coronaries
    - b Myocardial infarction due to
      coronary thrombosis
      coronary embolism
- B Myocarditis
- C Pericarditis

III Pain originating in other intrathoracic structures
- A Aorta
  - 1 Syphilitic aneurysm
  - 2 Dissecting aneurysm
- B Pulmonary artery—pulmonary embolism
- C Broncho pulmonary tree and pleura
  - 1 Pneumonia
  - 2 Pleuritis
  - 3 Empyema
  - 4 Tumors of bronchi lungs or pleura
  - 5 Pneumothorax
  - 6 Hemothorax
- D Mediastinum
  - 1 Mediastinal or interstitial emphysema
  - 2 Tumors of lymph nodes and other mediastinal structures
  - 3 Suppurative infections of lymph nodes and other mediastinal structures
- E Esophagus
  - 1 Tumors
  - 2 Infections
  - 3 Ulceration
  - 4 Diverticuli
- F Diaphragm

IV Pain referred from subdiaphragmatic structures
- A Peritoneum
- B Stomach
- C Pancreas
- D Liver and biliary tree
- E Spleen
- F Kidneys and perirenal tissues
- G Large bowel

V Neurotic pain and pain of obscure origin

PAIN ORIGINATING IN THE TISSUES OF THE NECK OR CHEST WALL

In seeking the cause of chest pain it is desirable first to give attention to the neck and chest wall Simple inspection or palpation may disclose the vesicles of herpes zoster scars involving sensory nerves tumors or abscesses of the breasts or other superficial structures paralysis of muscles pointing to involvement of the spinal nerves localized tenderness of bones or cartilages due to infection or to

nfiltration by tumors Valuable information may also be supplied by roentgenograms cervical ribs or other anomalies, tumors or infections of bone hypertrophic arthritis of the spine narrowing of intervertebral spaces due to extrusion of a disc widening of the vertebral foramina due to neurofibromas The type of pain experienced by the patient may be a guide to the location of the disease process With lesions of bone it is usually of a dull, sometimes throbbing character and is frequently worse in the evening, with lesions of the spinal cord and nerve roots it tends to be sharper and has a more clearly defined segmental distribution

No attempt will be made here to describe in detail the numerous diseases of the supporting tissues of the neck and chest wall which give rise to chest pain There are, however several syndromes which should be mentioned briefly because these symptoms may be confused with those produced by disease of the heart These syndromes should not be overlooked they have important therapeutic implications One is the variable symptom complex produced by extrusion of an intervertebral disc in the lower cervical region There are usually evidences of involvement of the cervical nerve roots depending upon the location of the disc The onset of the pain frequently follows trauma or some unusual stress upon the neck The intensity of the pain varies with movements of the neck and may be aggravated by jumping coughing and sneezing It may be relieved by extension or traction of the neck Secondly there is the scalenus anticus syndrome This is usually associated with a cervical rib or an unusually large transverse process of one of the lower cervical vertebrae It may also be due to hypertrophy of the scalenus anticus muscle The pain may be sharp or dull It usually follows the course of the median and ulnar nerves on the affected side, but it may extend upward to the shoulder and into the neck It is aggravated by rotation of the head or forceful downward traction on the shoulder There may be associated circulatory disturbances in the arm A tender swelling may be felt in the region of the scalenus muscle Adson s maneuver may cause the pulse to become weak or disappear on the affected side The two syndromes just described must be distinguished from the shoulder hand syndrome which occasionally follows myocardial infarction The shoulder hand syndrome is characterized at first by a painful disability of the shoulder and vasomotor disturbances in the arm and hand If the symptoms progress there may be atrophy of the skin muscles and bones of the arm and contractures of the hand

PAIN ORIGINATING IN THE HEART

As noted in Table 6 pain originating in the heart may be due to relative or absolute myocardial ischemia myocarditis or pericarditis

RELATIVE MYOCARDIAL ISCHEMIA Relative myocardial ischemia may result from low perfusion pressure (aortic insufficiency) diminished oxygen carrying capacity or oxygen saturation of the arterial blood (severe anemia) or increased cardiac demand for oxygen (exertion or thyrotoxicosis) The effect of each of these types of relative ischemia is enhanced if it is combined with some degree of absolute ischemia such as results from partial occlusion of coronary arteries Under these circumstances relatively slight changes in perfusion pressure, oxygen supply or oxygen demand may give rise to pain For example in patients with hypertension and coronary arteriosclerosis pain may not occur until some therapeutic procedure (such as sympathectomy) has reduced the diastolic pressure from a high level to a normal level Exertion may then cause pain typical of angina pectoris

ABSOLUTE MYOCARDIAL ISCHEMIA When one considers absolute ischemia the converse of what has just been stated is true If the absolute ischemia is due to partial obstruction of a coronary artery there may be no pain unless some of the factors leading to relative ischemia are superimposed These relationships are in fact responsible for the characteristic manifestations of angina pectoris in which pain may not occur until the cardiac demand for oxygen rises during exertion or emotional stress The exercise tolerance test and the anoxia test for coronary artery disease are based upon these principles

When the absolute ischemia is due to complete obstruction of a coronary artery the typical pain is continuous it does not require exertion for its production Nevertheless factors which promote relative ischemia may aggravate the pain and conversely factors which tend to reduce relative ischemia (e g administration of oxygen or raising the perfusion pressure) may ameliorate the pain

From what has just been said it becomes apparent that the pain of myocardial ischemia depends in many instances upon a combination of factors The difficulty in interpreting such pain and explaining it on logical grounds is increased by the fact that absolute ischemia leading to extensive myocardial infarction may in some cases give rise to no pain at all This serves to remind us again that pain is a poor feature for orientation of diagnosis It is wholly subjective and

its occurrence and intensity depend as much upon the sensitivity of the individual as upon the quality and quantity of the causative stimulus

The term *angina pectoris* as employed here refers to pain attributable to partial obstruction of the blood flow through the coronary arteries It is sometimes called the angina of effort although it may be induced by factors other than effort There is no associated myocardial infarction The pain of angina pectoris usually follows a characteristic pattern so fully described in many other publications that the description need not be repeated here Typically the pain subsides when the inciting stimulus is removed Subsidence of the pain is promoted by the use of nitrites

Myocardial infarction the most important of the conditions included among the causes of cardiac pain is usually accompanied by objective as well as subjective manifestations But the objective findings may also cover a very wide range In one case there may be instant death In another patient no more than debatable deviations from normal may be discovered upon examination of the cardiovascular system The effect of occlusion of a coronary artery may be great or small depending not only upon the size and location of the artery involved but upon the state of the other coronary arteries and the number of collateral channels which may be brought into play Anastomoses in the coronary circulation become more extensive and more effective with advancing years Other things being equal the heart of a man of 60 years is better prepared to withstand the effects of coronary occlusion than is the heart of a man of 30 The extent of the infarction doubtless depends not only upon the age of the patient but upon the rapidity with which the artery becomes occluded When occlusion progresses slowly over a period of weeks or months there is obviously a greater opportunity for development of collateral channels before the occlusion becomes complete The effect of the coronary occlusion upon the conducting mechanism of the heart is also important Ventricular fibrillation may occur almost immediately and lead to sudden death Another peculiar variant in the classic symptoms of coronary occlusion is that pain may not occur when the occlusion develops in the presence of myocardial insufficiency Under these circumstances there may be merely an increase in previously existing dyspnea and cyanosis

The manifestations of coronary occlusion with myocardial infarction may be divided into three groups (1) the immediate symptoms, (2) disturbances in cardiac function and (3) evidences of injury to myocardial tissue

IMMED ATE SYMPTOMS The major symptoms occurring immed ately are pain and evidences of shock such as prostration sweatin nausea and fall in blood pressure All of these may appear with gre suddenness The pain of coronary occlusion may have the same di tribution as that of the angina of effort but it is more prolonged ar usually more severe It frequently differs from the pain of angi pectoris in its tendency to be more circumscribed and to appear unusual locations such as the epigastrium and the interscapular are When localized in the epigastrium the pain may be accompanied b tenderness and rigidity of the abdominal muscles If nausea an vomiting are also present the picture may closely simulate that of a acute intra abdominal catastrophe Occasionally there is no true pai merely a feeling of numbness or oppression or a sense of grea difficulty in breathing In the typical angina of effort the patient usu ally assumes an attitude of immobility he is afraid to move Th may also be the case with coronary occlusion but in many instance there is a restless activity—apparently an effort to escape agony an bewilderment The fall in blood pressure which in cases of sever myocardial infarction may persist for days or even indefinitely ma be helpful in distinguishing this condition from both angina pectori and dissecting aneurysm of the aorta in which the pain is usuall accompanied by a rise in blood pressure

DISTURBANCES IN CARDIAC FUNCTION Disturbances in cardia function may take a variety of forms Direct examination of the hear may disclose no abnormality or there may be some feebleness of th pulsations and heart sounds and a gallop rhythm may be present There may be minor or major disturbances in rhythm of which th most ominous originate in the ventricles with progression from ven tricular premature contractions to ventricular tachycardia to ventric ular fibrillation There may also be various types of supraventricula arrhythmia and variable degrees of heart block With the passage o time depending upon the extent of the damage to the myocardium signs and symptoms of myocardial insufficiency may develop dysp nea cyanosis chronic passive congestion These may appear within several hours or they may not be evident until long after the initial episode at the time when the patient is attempting to resume his normal activities

EVIDENCES OF INJURY TO MYOCARDIAL TISSUE Evidences of injury to myocardial tissue may be either remote or local The remote evidences are those which may be observed with any type of serious tissue injury fever leukocytosis and elevation in the erythrocyte

hours of the initial event and, depending upon the extent of the injury may persist for a variable number of days Another remote evidence of injury to the myocardium comes somewhat later in the form of embolic phenomena The emboli arise from mural thrombi which form at the site of injury When they originate in the right ventricle pulmonary infarction results When they originate in the left ventricle there may be various peripheral or visceral embolic phenomena A pericardial friction rub may provide the best local evidence of myocardial injury These rubs usually appear several days after the initial injury They may be localized to a small area, may be very faint may come and go or may have a total duration of only an hour or two They will usually not be heard unless the heart is examined repeatedly and with great care Therefore, the failure to discover a pericardial friction rub has little diagnostic significance while its detection may provide in some cases the only definite evidence of myocardial infarction

As a means of demonstrating local myocardial injury the electrocardiograph is our most valuable instrument Modern electrocardiographic technique not only enables us to make an unequivocal diagnosis of myocardial infarction in the majority of cases but it may provide information concerning the precise location of the injury Electrocardiograms should be interpreted only within the setting of the clinical findings Electrocardiographic changes due to digitalis pericarditis acute myocarditis pulmonary embolism and dissecting aneurysm of the aorta may closely simulate those of myocardial infarction On the other hand in some cases of myocardial infarction the electrocardiogram may be normal or the typical changes may be obscured by a pre existing cardiac disturbance such as bundle branch block The interpretation of electrocardiograms is less subject to error if generous use has been made of multiple leads and if the procedure is repeated at intervals during the illness Serial electrocardiograms exhibiting the typical evolution of a myocardial infarct provide almost incontrovertible evidence if the clinical findings are in any way consistent with this diagnosis

The diagnosis of myocardial infarction is usually not difficult if the initial episode is severe and if the patient survives long enough to develop the characteristic clinical and electrocardiographic signs of injury to the myocardium In some cases however the initial episode is mild It may have passed unnoticed or it may have been mistaken for a minor gastrointestinal or pulmonary incident The first symptoms appearing some days or weeks later, may be those of myo

cardial insufficiency The sudden onset of cardiac failure for which no other explanation can be found should always awaken suspicion of a myocardial infarction The electrocardiogram may be very helpful in the interpretation of such cases

Complete coronary occlusion is usually due to thrombosis in scle rotic arteries It occurs more often in men than in women In women it is more frequently associated with hypertension Although myo cardial infarction is typically a disease of older people numerous cases have been reported in recent years in individuals between 30 and 40 years of age

Occlusion of the coronary arteries may be due to disease of the aorta when the coronaries themselves are relatively free of disease Syphilitic aortitis may cause obstruction by compressing and sealing over the mouths of the coronaries A dissecting aneurysm may have a similar effect

Embolism may also be a cause of coronary occlusion The emboli may arise from six possible sources

(1) Atheromatous material in a coronary artery itself
(2) Thrombus from an atherosclerotic plaque at the base of the aorta
(3) Bacterial vegetations from the mitral or aortic valve
(4) Intracardiac mural thrombi
(5) Thrombi in pulmonary veins
(6) Thrombi in peripheral veins—paradoxical embolism

Almost half of the recognized cases of coronary embolism are attrib utable to bacterial vegetations on the mitral or aortic valve Death from coronary embolism is in most instances very sudden but one observes occasional cases in which multiple emboli by obliteration of many small coronary branches have led to diffuse scarring of the myocardium and gradual heart failure The two conditions in which we have seen multiple small coronary emboli are bacterial endocar ditis and intracardiac thrombosis

PERICARDITIS In most cases the pain of *acute pericarditis* is de scribed as a dull ache combined with a feeling of substernal pressure At times it is severe and may be extraordinarily difficult to distinguish from pain due to myocardial infarction Capps and Coleman have shown experimentally that only a portion of the parietal pericardium is at all sensitive to painful stimuli The pain in pericardial disease usually arises in the adjacent pleura The symptoms may be mistaken for those of an acute pleurisy When the pericardium contiguous with the central portion of the diaphragm is inflamed the pain may be

referred to the shoulder The same may be true when there is occlusion of the right coronary artery resulting in a posterior type of myocardial infarction In some cases the pain of acute pericarditis so closely simulates that of myocardial infarction that it has been suggested that pericardial inflammation leads to reflex spasm of the coronary arteries An accompanying pleuritis, common with primary pericarditis but rare with myocardial infarction may be a helpful differential factor In some cases when pericarditis involves the diaphragmatic area there may be severe upper abdominal pain and rigidity of the abdominal muscles The friction rub of acute pericarditis is usually heard over a wide area and owing to the involvement of adjacent pleura it may be related to respiratory as well as cardiac movements Only rarely does the friction rub of myocardial infarction possess these characteristics Occasionally the timing and acoustic qualities of a pericardial friction rub may mimic very closely the soft to and fro murmur of aortic insufficiency

PAIN ORIGINATING IN OTHER INTRATHORACIC STRUCTURES

No attempt will be made to describe in detail all of the conditions which might be included under this heading Particular attention will be paid to the diseases giving rise to pain frequently confused with that of myocardial infarction

The pain of *dissecting aneurysm* of the aorta is usually more prolonged and constant than that of myocardial infarction It may be located beneath the sternum in the interscapular region throughout the anterior portion of the chest or in the abdomen Extension of the pain from its original location may be determined by the extent and direction of the dissection The pain may extend into the head neck arms thorax abdomen or lower limbs It may suddenly disappear if the aneurysm establishes a new communication with the main lumen of the aorta Shock fever, and leukocytosis are usually less marked than with myocardial infarction Although embolism does not occur the dissection of the arterial coats, for example of the carotid subclavian renal or inguinal arteries may lead to occlusion of vessels closely simulating that caused by emboli Leakage of blood into the pericardial cavity may give rise to a friction rub suggesting myocardial infarction or acute pericarditis An aortic diastolic murmur attributable to widening of the aortic ring with resulting relative aortic insufficiency is heard in many cases of dissecting aneurysm Murmurs may also be heard over arteries which have been

partially occluded by the dissection or at points where new communications have been established between the aneurysm and the main lumen of the aorta

Dissecting aneurysm occurs more frequently in men than in women Although the break in the aorta is frequently attributed to disease of the aorta *it is rarely observed in individuals who do not have an* antecedent history of either permanent or temporary arterial hypertension In most instances in which blood pressure was recorded shortly before and after dissection there appeared to be a moderate drop in the pressure But even after such drop the pressure usually remains at hypertensive levels Evidences of shock may be observed while the blood pressure is high or within normal limits Rarely does one see the extremely low levels of blood pressure which are so frequently *encountered in cases of myocardial infarction*

Diseases of the broncho pulmonary structures pleura and mediastinum will be discussed in other chapters The conditions which chiefly concern us here are pulmonary infarction pneumothorax and mediastinal emphysema

In *pulmonary infarction* resulting from embolism the pain may be attributed to one or more of the following factors (1) pleuritis over the area of infarction (2) reflex diminution in coronary blood flow (3) *a disturbance in the pulmonary artery itself Electrocardiograms* may show changes indistinguishable from those of myocardial infarction The associated symptoms and signs may also be difficult to distinguish There is usually sudden pain followed by collapse and later by fever and leukocytosis When the left lower lobe is infarcted there may be a pericardial friction rub The factors which are particularly helpful in making a diagnosis of pulmonary infarction are demonstration of a source of possible emboli cough with expectoration of blood *definitely pleuritic type of pain pleural friction rub* and characteristic shadows in the x ray pictures of the chest

Although the pain of an acute pneumothorax and the accompanying dyspnea and prostration may lead to suspicion of myocardial infarction adequate examination of the chest usually leads to a correct diagnosis without much delay Characteristically the acute pain is followed by a feeling of tightness in the chest which may sometimes be located by the patient in the affected side Although the physical signs of pneumothorax are usually clear cut the definitive diagnosis in most instances depends upon the x ray findings

Mediastinal emphysema which has been so well described by Hamman may give rise to severe pain closely simulating that of myo-

cardial infarction The correct diagnosis depends upon both positive and negative factors There is a peculiar crackling sound synchronous with the heart beat This can usually be heard best along the left sternal border Sometimes it is so loud that it can be heard by the patient himself In addition to the auscultatory phenomena there may be palpable subcutaneous crepitations and air may be seen in the mediastinum on radiological examination

With mediastinal tumors the type and location of pain vary with the position and nature of the lesion With masses in the anterior mediastinum the pain is usually retrosternal Tumors in the posterior mediastinum are frequently neural in origin erode bony structures, and produce a boring continuous type of discomfort With acute mediastinitis, or with mediastinal abscess due to tuberculosis or syphilis or secondary to esophageal disease, the pain may radiate to the back or upward to the shoulder region Superficial tenderness on pressure is common and occasionally crepitations are audible

Pain associated with esophageal disease is usually due to some type of obstructive lesion with resulting increase in the intraluminal pressure Associated complaints such as relation of pain to meals dysphagia and regurgitation of undigested food particles are helpful in making a diagnosis

PAIN REFERRED FROM SUBDIAPHRAGMATIC STRUCTURES

The pain and other manifestations of disease of certain abdominal viscera may be mistaken for symptoms of cardiac origin The pathways by which pain arising in intra abdominal organs is referred to the chest are not clearly understood A diaphragmatic hernia may give rise to paroxysmal substernal pain of a constrictive type It may occasionally be sharply differentiated from cardiac pain by its prompt disappearance when the patient sits up The location of the pain of peptic ulcer may sometimes suggest cardiac pain but it may usually be recognized by its relation to meals rather than to exertion Acute pancreatitis may give rise to severe pain and shock suggesting myocardial infarction However the pain usually radiates to the back The blood amylase determination may be the clue to the correct diagnosis Cholelithiasis and cholecystitis are particularly likely to cause a misleading set of symptoms Under certain circumstances the discomfort caused by cholelithiasis seems to act as a trigger mechanism for angina pectoris Dr Francis F Harrison has been particularly interested in this subject and has records of a number of cases in

which the removal of a gallbladder containing stones brought an end to a series of what appeared to be anginal attacks extending back over a period of months or years before operation Steincrohn called attention to the importance of the rhythm and periodicity of the pain in distinguishing acute cholelithiasis from myocardial infarction In myocardial infarction the pain is not of a colicky type but may be made up of severe paroxysms interrupted by periods when the pain though still present is much less intense

Illustrative Cases

I

(#311911 Admitted Jan 19 1944 Died Jan 24, 1944)

THIS 36 year old Negro housewife complained of epigastric pain of 12 hours duration She had noted exertional dyspnea for six years with mild orthopnea

She was seen in April 1930 complaining of pain and swelling in the knees for one month The right knee was swollen with increase in skin temperature and grating on motion The Wassermann reaction was positive A diagnosis of infectious arthritis was made She returned in 1932 complaining of pain in the left knee On examination a blowing systolic murmur was heard in the aortic area The blood pressure was 180/100 A diagnosis of syphilitic aortitis was made The spinal fluid was normal She returned again in 1937 complaining of pain in the left knee The cardiac findings were the same blood pressure being 162/100 Urine examination showed a trace of albumin During this period she was seen on one occasion with generalized urticaria and abdominal pain The blood pressure at that time was 155/88

On January 19 1944 she suddenly developed pain in the epigastrium radiating to the interscapular region The pain was intermittent in character lasting for 25 to 30 minutes with freedom between attacks for several moments There was no nausea vomiting abnormality in bowel function or urinary symptoms There had been no similar attacks previously

PHYSICAL EXAMINATION on admission T 100 4 P 100 R 32 B P 265/124

The patient an obese woman was moaning and holding her abdomen There was no lymph node enlargement Respirations were rapid but the lungs were clear There was enlargement of the heart to the left The rate was rapid but the rhythm was regular The sounds were of fair quality A blowing systolic murmur was audible over most of the precordium maximal at the base The abdomen was obese There was increased muscle tone and generalized tenderness with referred pain to the epigastrium on pressure over the lower abdomen with rebound tenderness There was marked tenderness to pressure in the epigastrium The extremities were normal Neurological examination revealed no abnormalities

COURSE IN THE HOSPITAL. The patient was digitalized and the following morning a laparotomy was done Following this the temperature

remained between 100 and 102 with pulse rate varying from 100 to 120 She was restless and perspired profusely Each time she was taken out of the oxygen tent she had marked dyspnea with shallow excursions Numerous tracheal rales were described The abdomen remained tender but she did not complain of pain She seemed to be improving then died suddenly

LABORATORY DATA Wassermann reaction positive hemoglobin 11 5 gm leukocytes 20 000 Urine examination showed specific gravity 1 026 albumin and sugar negative 9–10 white cells and 3–4 red cells per high power field with no casts Blood nonprotein nitrogen 28 mg % bilirubin less than 0 8 mg % total protein 7 5 gm % Electrocardiogram on January 19 showed normal sinus rhythm left axis deviation Marked sagging of the S T segments in all leads Initial upward deflection in the chest lead Record showed evidence of left sided enlargement and digitalis effect

DISCUSSION This patient was considered by the internists and surgeons who saw her to have an acute abdominal emergency and was operated upon within a few hours after admission the preoperative diagnosis was acute cholecystitis and cholelithiasis The operative findings were not revealed to the discussor The first problem seems to be whether the primary cause of the pain was above or below the diaphragm This is often difficult to determine as it is well known that coronary thrombosis pulmonary embolus or pneumonia in the lower lobes may present signs and symptoms pointing strongly to the presence of some acute abdominal condition The pain in this case was felt in the epigastrium but was severe between the scapulae dyspnea was an outstanding symptom The onset was precipitous and there was no history of any preceding attacks of pain or of any gastrointestinal symptoms nor were any gastrointestinal symptoms described in the final illness The pain and the maximum degree of tenderness were in the midline—between the scapulae and in the epigastrium These facts lead one to suspect that the difficulty was above and not below the diaphragm

Several intra abdominal conditions may be considered further however Acute hemorrhagic pancreatitis is an obvious possibility A shocklike picture which was not present in this case is sometimes seen and pain high between the scapulae would be unusual Acute cholecystitis or empyema of the gallbladder must be considered The pain was unusually severe and persistent the degree of dyspnea incompatible and the location of the pain and tenderness atypical There was obviously no common duct obstruction by stone Rupture of a peptic ulcer into the lesser peritoneal sac is possible but the pain should be lower down the tenderness more localized and dyspnea and excessive elevation of blood pressure would not be expected

The other possibilities are related to vascular disease With the severe hypertension and with the record of some fluctuation in blood pressure on previous visits one might consider paroxysmal hypertension from a pheochromocytoma A careful look at the symptoms leads one to discard this idea The recurrent pain in the knees, the attack of urticaria with abdominal tenderness and the hypertension with epigastric pain suggest the possibility of periarteritis nodosa with mesenteric thrombosis or acute lesions in the pancreas, stomach, or gallbladder, but that would put unnecessary emphasis on rather uncommon events, the knee pain was probably related to her obesity, and the hives to something she ate

Now that a variety of subdiaphragmatic conditions have been considered and no attractive possibility unearthed what intrathoracic disease might this be? Pulmonary embolism might have such a sudden onset and the source in a fat woman with hypertension could be either intracardiac or peripheral The location of the pain would be unusual for an embolus large enough to cause such distress—it should be more prominent anteriorly The subsequent course of events revealed nothing to suggest this diagnosis In a fat woman with syphilis and hypertension the two best possibilities, and the most difficult to distinguish between with the information available are coronary insufficiency on an arteriosclerotic or syphilitic basis and a dissecting aneurysm beginning just beyond the arch of the aorta

In the presence of both syphilis and hypertension with probable arteriosclerosis it is difficult to tell which is the cause of coronary disease It can sometimes be correctly predicted if symptoms of coronary insufficiency with pain have been present for a period of time The pain due to encroachment of syphilitic aortitis upon the coronary ostia may produce a suggestive clinical picture in that the pain is likely to appear more frequently at rest and to be more persistent The presence of aortic insufficiency would also suggest syphilis In this case there is no history of any previous attacks With either syphilitic stenosis or coronary thrombosis on an arteriosclerotic basis one would expect pain higher in the chest with more substernal localization If the attack were severe enough to cause such discomfort with fever and leukocytosis the blood pressure should not be at such an exaggerated level as it was in this case The single electrocardiogram available shows only the changes one would expect with this degree of hypertension

With a dissecting aneurysm the pain is usually sudden in onset and intense Sometimes it appears first in the interscapular region or in

the abdomen The pain has a wider radiation in most instances than that of coronary thrombosis rarely extends to the arms and it is more likely to be persistent than is the pain of coronary occlusion Pre existing hypertension is the rule and even when the patient is prostrate with pain the blood pressure frequently remains up or rises to very high levels Fever and leukocytosis are usually present The most significant point against this diagnosis is the possible presence of syphilitic aortitis which supposedly tends to protect against dis section but on the whole it seems the most likely cause of the patient s illness If one assumes that the diagnosis of dissecting aneu rysm is correct then rupture into the pericardium pleura or even into the abdominal cavity was probably the terminal event

Anatomical Diagnosis (Autopsy No 18742) Arteriosclerosis and arteriolosclerosis Dissecting aneurysm of aorta from just below the left subclavian mouth down into the left common iliac with rupture into left pleural cavity Left hemothorax Pulmonary emphysema Cardiac hyper trophy History of hypertension Diffuse intrarenal arteriosclerosis with slight scarring of kidneys Surgical absence of gallbladder and cystic duct

All chambers particularly the left ventricle were hypertrophied The wall of the aorta had been dissected apart from the orifice of the left sub clavian past the bifurcation of the aorta At a point about 2 cm distal to the obliterated end of the ductus arteriosus in the right part of the wall of the aorta there was a hole 7 by 3 mm which opened from the outer layer of the aneurysm to the tissues of the mediastinum In this neighborhood the tissues were full of blood clots and there was 700 ml of freshly clotted blood in the left pleural cavity On microscopic section the splitting of the media was that typically seen in dissecting aneurysm There was marked narrowing of the intrarenal arteries and extreme arteriolosclerosis espe cially about the adrenals

Summary This 36 year old Negro woman was known to have hyper tension for 12 years The day of admission she developed sudden epigastric pain radiating to the interscapular area Examination revealed hyperten sion cardiac enlargement a systolic bruit and abdominal tenderness most pronounced in the epigastrium with increased muscle tone and rebound tenderness A cholecystectomy was performed and she died suddenly four days later Consideration of the findings suggested disease originating above the diaphragm most likely cardiovascular in nature The character and location of the pain the persistence of hypertension and the absence of electrocardiographic changes suggestive of myocardial infarction led to a diagnosis of DISSECTING ANEURYSM which was confirmed by the autopsy Death was due to rupture into the left pleural cavity

II

(#392705 Admitted July 19 1946 Died July 26 1946)

THIS 43 year old Negro domestic complained of severe pain beneath the sternum and shortness of breath of one hour s duration At age 29 she was found to have a positive serologic test for syphilis and had received treat ments for two months

Six years before admission she began to have headaches and was told that she had hypertension (systolic as high as 240) In January 1946 she first noted a feeling of tightness in the epigastrium and beneath the sternum which came on particularly after climbing stairs There was accompanying dyspnea and a tight feeling in the throat The symptoms disappeared after rest In February 1946 while housecleaning she suddenly experienced a crushing pain in the epigastrium and beneath the sternum which radiated into the left side of the neck and jaw She stopped work but the pain did not disappear immediately as the previous attacks had The following day she attempted to work but had a recurrence of the pain associated with short ness of breath At this time she resumed anti syphilitic therapy The attacks of dyspnea on exertion accompanied by substernal and epigastric pain continued

The day of admission while riding on a bus she was seized without warning by a crushing pain beneath the sternum which radiated to the left chest but not into the neck or arm It became difficult for her to breathe and she was very apprehensive She felt nauseated but did not vomit When she arrived at the hospital her extremities were cold the heart sounds were barely audible and the blood pressure was 110/60 dropping rapidly to 90/40

PHYSICAL EXAMINATON on admission T 99 6 P 100 R 26

The patient was a well developed moderately obese Negro woman The pupils were small equal but slightly irregular and did not react to light (morphine had been administered) The fundi showed narrowed arteries but no hemorrhages or exudates were seen The trachea was in the mid line The cervical veins were full The lungs were clear The point of maximal impulse of the heart was 9 5 cm to the left of the sternum in the 5th interspace The rhythm was regular The apical first sound was sharp but distant In the third interspace to the left of the sternum a soft early diastolic murmur was heard The liver edge was palpable on deep inspira tion The reflexes were equal and active There was no edema

COURSE IN THE HOSPITAL The temperature ranged from 100 to 103 4 and there was a concomitant increase in pulse rate The boring

substernal ache persisted in spite of morphine The blood pressure gradually rose to 140/60 On the 4th hospital day the patient had a severe exacerbation of pain which lasted for thirty minutes although she was given morphine On July 22 the heart was described as greatly enlarged both to the left and right of the sternum with a visible and palpable impulse in the 5th interspace A diastolic murmur was heard loudest to the right of the sternum The pulse was of the Corrigan type On July 26 she suddenly became unresponsive and developed conjugate deviation of the head and eyes to the left The pulse could not be felt Blood pressure was 55/0 The heart sounds were audible in the pauses between respiration being regular but of poor quality There was no further increase in the area of cardiac dullness Death occurred shortly after onset of this episode

LABORATORY DATA Serologic test for syphilis negative urine normal leukocytes 10 640 with 82% polymorphonuclears 15/ lymphocytes 4% monocytes and 1% basophils sedimentation rate 25 mm per hour hemoglobin 13 gm Electrocardiogram on July 19 showed a P R interval of 0 16 sec rhythm normal P waves normal QRS 3 inverted tendency to left axis deviation T1 2 and 4 upright T3 inverted S T segments normal On July 22 electrocardiogram showed that since July 19 T2 had become isoelectric and T4 inverted There was slight elevation of ST3 and ST4 was slightly depressed Changes were definite and suggested the evolution of some acute process She had received no digitalis No x ray examinations were made

DISCUSSION The physician is often confronted with the problem of a patient with collapse following the onset of severe pain in the chest At the present time when almost every sudden severe pain in the chest in individuals past or in middle age is at once called coronary occlusion it is well to emphasize that there are other diseases of the cardiovascular system the lungs and the abdominal organs which may so closely resemble coronary occlusion that they are distinguishable from it only with difficulty

In the present case the attacks of substernal pain appearing after exertion over a period of months and the findings on examination of the heart leave little doubt that this patient s illness was the result primarily of disease of the cardiovascular system

She had syphilis with evidences suggesting insufficiency of the aortic valve There was also a history of hypertension and on examination the retinal vessels were found to be narrow

Four major possibilities will be considered all of which could produce the pain with a picture of shock the aortic insufficiency and the sudden death (1) bacterial endocarditis engrafted on an aortic valve previously damaged by syphilis (2) dissecting aneurysm of the aorta (3) arteriosclerotic disease of the coronary arteries with cor

onary thrombosis, (4) syphilis of the aorta with narrowing of the coronary ostia and syphilitic aortic insufficiency

(1) Bacterial Endocarditis Engrafted on an Aortic Valve Previously Damaged by Syphilis Anginal pain is not uncommon in the presence of aortic insufficiency, and the acute substernal pain with shock on the day of admission could have been caused by lodging of a friable vegetation in a coronary artery About 50% of coronary emboli are seen in patients with subacute bacterial endocarditis Cerebral embolization is also common in this disease when the aortic valve is involved but death is not usually as sudden as in this case The absence of symptoms of infection before the final illness and the lack of anemia petechiae clubbing of the fingers and enlargement of the spleen are all against this possibility It would be a rare sequence of events

(2) Dissecting Aneurysm of the Aorta This is most commonly seen in patients with hypertension It must be considered as a possibility when severe pain in the chest with shock are the presenting symptoms there is evidence of aortic valve involvement, and sudden death occurs The pain in these cases usually begins in the chest and progresses to the epigastrium and lower abdomen which was not true in this patient Altered pulsation in one of the major peripheral vessels is commonly but not uniformly present If this disease explains the terminal illness in this patient one would also expect to find arteriosclerotic disease of the coronary vessels to account for the previous attacks typical of angina pectoris Rest would hardly be expected to have terminated them had they been associated with hemorrhage and dissection in the medial layer of the aorta The terminal event is often rupture into the pericardium but in this case the enlargement of the area of precordial dullness was not associated with the sudden exitus but preceded it by several days

(3) Arteriosclerotic Disease of the Coronary Arteries with Coronary Thrombosis There are many of the features of this picture which fit well with such a diagnosis The history of hypertension the typical attacks of substernal pain following exertion and relieved by rest with a final episode of more severe pain which occurred without exertion with shock low blood pressure subsequent fever and finally sudden death six days later are all quite typical However the occurrence of as severe an attack as this without more typical electrocardiographic findings and also the presence of the signs of aortic insufficiency lead one to search further among the possibilities

(4) Syphilis of the Aorta with Narrowing of the Coronary Ostia

and Syphilitic Aortic Insufficiency Syphilis invades the mouths of the coronary arteries and alterations in the course of the artery are unusual in contrast to the situation in arteriosclerosis The process is gradual and terminally there may be complete obliteration of the *mouths of one or both coronary arteries Actual thrombosis may not* take place In this case we have a woman with inadequately treated syphilis who developed attacks of anginal pain which increased in severity with a final attack which was not accompanied by the typical electrocardiographic findings of coronary thrombosis In view of the fact that *syphilitic aortitis progresses slowly time for the develop* ment of collateral circulation is allowed Under these circumstances one seldom sees repeated attacks of angina pectoris occurring over a long period of time and followed by a terminal event suggesting coronary occlusion Nevertheless although arteriosclerotic coronary disease is more common the definite aortic insufficiency and the severe precordial pain without striking electrocardiographic changes of infarction incline one to consider syphilis as the major factor in this case Sudden death is common in cases of this type and may be the result of ventricular fibrillation

ANATOMICAL DIAGNOSIS (Autopsy No 20061) Syphilitic aortitis Syphilitic aneurysm of ascending aorta with previous leakage and terminal rupture into the pericardial sac Pericardial adhesion Focal areas of myocardial atrophy and scarring Focal areas of hemorrhage in lung Ductal adenoma of pancreas Calcification and bone formation in dura Chromophobe adenoma of hypophysis

The potential free space of the pericardial cavity was obliterated by dark blood clots and adhesion The pericardium was adherent and thickened over the ventricular surface of the heart and there was much old blood pigment in the adhesion Over the auricles there was old as well as fresh hemorrhage The heart cavities all appeared compressed The aortic valve showed some thickening of all its cusps Arising from the anterior surface of the ascending aorta about 1 cm above the sinuses there was a saccular aneurysm the wall of which was thinned out and which contained little thrombus material It had ruptured into the pericardial sac

This was a case of classic syphilitic aortitis with extensive medial changes seen on microscopic examination of the section Apparently the aneurysm had leaked slowly into the pericardial cavity on repeated occasions and *then there was a final rupture with death* This accounts for the appearance of pain at rest and for its severity and persistence

SUMMARY This 43 year old Negro female was known to have inade quately treated syphilis for 14 years Six years before admission hyper tension was first noted Six months before death she developed attacks of substernal oppression and exertional dyspnea The pain was not always relieved by rest and the day of admission an attack of severe pain was

followed by hypotension There was venous engorgement and an aortic diastolic murmur was noted The pain persisted and there was fever The heart became greatly enlarged and she died suddenly The electrocardiogram did not show changes typical of myocardial infarction The coronary insufficiency was thought to be due to syphilis SYPHILIS OF THE AORTA was found at autopsy but the basic lesion was a small SYPHILITIC ANEURYSM arising just above the base of the heart with previous leakages and terminal rupture into the pericardial sac More attention should have been paid to the evident venous engorgement and the marked enlargement of the area of precordial dullness

III

(#67483 Admitted January 27 1936 Died February 3 1936)

THIS 28 year old Negro laborer entered complaining of pain over the left lower ribs hiccups and vomiting Three years before he was stabbed in the same location as the pain of which he complained No serious symptoms had followed the stab wound On the morning of admission his wife awakened him suddenly He was startled jumped from bed and immediately complained of excruciating pain over the left lower ribs He began to vomit and had violent hiccups These difficulties continued throughout the day

PHYSICAL EXAMINATION on admission T 101 6 P 140 R 26 B P 110/66

The patient was apprehensive and complained bitterly of the pain There was mild dyspnea The left chest was held immobile Every other breath was accompanied by hiccups During the examination the patient vomited 300 ml of black bloody material At the lower border of the ribs was the scar of the stab wound received three years before The pupils reacted normally The trachea was in the midline there was no tug There was no lymphadenopathy and the thyroid was normal The right lung showed nothing abnormal On the left there was dullnes below the angle of the scapula and diminished breath sounds Over the precordium there was a high pitched pleuro pericardial sound The exact position of the heart could not be determined There was a systolic murmur at the apex The second pulmonic sound was accentuated The pulse was rapid and regular The abdomen was soft There was tenderness in the left upper quadrant No organs or masses were felt The reflexes were normal

COURSE IN THE HOSPITAL A needle was inserted in the 4th interspace left mid axillary line and 20 ml of bloody fluid was withdrawn which showed a hemoglobin content of 64/ and 80 000 leukocytes per cu mm The patient vomited dark blood on frequent occasions His temperature remained above normal the pulse rate was rapid and the blood pressure steadily fell Vomiting and hiccups persisted He grew steadily weaker and died seven days after admission

LABORATORY DATA On January 27 hemoglobin was 110/ leukocytes 8 760 On February 1 hemoglobin was 82/ Wassermann reaction was strongly positive Urine examination was normal The temperature varied from 100 4 to 104 6 the pulse rate from 120 to 160 Roentgenogram of the chest showed a dense shadow occupying the left base with some apparent shifting of the mediastinal structures to the right Three days later a second film showed that the area of clouding was higher There

was a region of relative translucency within the clouding which suggested either extreme elevation of the diaphragm or a diaphragmatic hernia although fluoroscopically with the patient supine barium demonstrated the stomach to be in normal relationship to the other organs in the abdomen

DISCUSSION The very sudden onset of the pain, its excruciating character the localization in the left chest, and the finding of bloody material on pleural tap suggest the possibility that the acute episode was cardiovascular in nature with conceivably rupture of a syphilitic or a dissecting aneurysm into the left pleural cavity, or a pulmonary embolus with infarction of the lung

However when one reviews the situation in detail there are certain associated findings which would not be logically explained by any of these diagnoses Vomiting was just as prominent a symptom as was the pain and during the entire week of illness the patient could not retain food In addition from the description of the vomitus there seems little doubt that hemorrhage into the gastrointestinal tract occurred Also the prominence of hiccup suggested involvement in the region of the diaphragm

Thus it would be more reasonable to conclude that in all likelihood the underlying disease must be one which can involve both the gastrointestinal tract probably the stomach, and also the left pleural cavity In searching for possibilities which could lead to involvement both above and below the diaphragm, the most important clue, particularly in the absence of any history of gastrointestinal symptoms previously would seem to be the history of a stab wound in the left chest three years before the present illness It seems perfectly possible that there could have been a diaphragmatic injury at that time with subsequent intermittent herniation of the stomach into the thoracic cavity This would be most likely to occur with the patient in the recumbent position and the acute attack just on awakening could conceivably be the result of sudden strangulation The strong point against this suggestion is the fact that the x ray study showed the stomach to be normal in contour and position

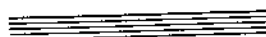
It is difficult to decide the exact nature of the lesion in this case, but hernia of the stomach through the diaphragm would seem most likely Leakage of an aneurysm into the left pleural cavity is difficult to rule out

ANATOMICAL DIAGNOSIS (Autopsy No 14638 partial) Strangulated diaphragmatic hernia of stomach in left pleural cavity Bloody fluid in left

pleural cavity fibrinous pleurisy (left) Atelectasis and lobular pneumonia of left lower lobe of lung Central atrophy and necrosis of liver Acute splenic tumor Dilatation of the pancreatic ducts Metaplasia of duct epithelium Pyelitis cystica

The left pleural space was found to contain 700 ml of dark bloody fluid which had a vile odor The cavity was lined with thick greenish exudate and there were adhesions at the posterior part of the lung The left lung was compressed upward and inward toward the hilum After the lung and the pleural fluid were removed there remained a large mass which had herniated through the diaphragm There was an opening in the diaphragm about 3 cm in diameter through which the middle portion of the stomach protruded The wall of the stomach in this area was infarcted and gan grenous It was filled with clotted blood The diaphragm was covered by fibrinous exudate so that the relationship of the defect to the old stab wound could not be established However the stomach and omentum were firmly adherent to the margins of the opening so that the herniation had been present a long time and the recent attack marked the onset of strangulation The microscopic sections showed a completely necrotic stomach wall Leakage through the necrotic stomach wall resulted in the relatively fresh blood in the pleural cavity

SUMMARY This 28 year old Negro laborer had been stabbed in the left lower axilla three years previously The morning of admission he was startled from sleep developed excruciating pain over the left lower chest began to vomit and had singultus The left chest was immobile there were signs of pleural fluid and a pleuro pericardial friction rub There was tenderness in the left upper quadrant He vomited changed blood Almost pure blood was aspirated from the pleural cavity X ray of the chest showed shift of the mediastinal structures and a suggestive area of trans lucency in the clouding at the left base was noted With barium the stomach seemed in normal relationship to the other organs The manifestations suggested involvement of both the gastrointestinal tract and the pleural cavity It was thought that injury to the diaphragm from the stab wound had allowed the stomach to herniate and that in the absence of previous symptoms the severe pain was due to strangulation This proved to be the case for at autopsy there was a STRANGULATED DIAPHRAGMATIC HERNIA OF THE STOMACH



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Chapter 4

SUDDEN DEATH

ANY PRACTICING PHYSICIAN may be called upon to express an opinion regarding the cause of sudden death in one of his patients or in a stranger who happens to die while travelling through his neighborhood Such an opinion is often superfluous but occasionally it is of practical importance In either circumstance it serves to emphasize the value of deductive reasoning based on a careful analysis of the known antemortem events viewed in the light of the probable causes of sudden death From a practical point of view as Hamman pointed out it is important as a first step to exclude trauma and poisoning As an example he cited the case of a vigorous man of 50 who while returning from an active summer vacation suddenly pressed his hand to his heart and died instantly It seemed reasonable to conclude that death had resulted from coronary occlusion and this diagnosis was officially entered as the cause of death Later in going over the insurance policies it was found that the estate would have been greatly increased had death been due to an accident It was then recalled that ten days before demise he had cut his right shin The abrasion had been sore for a few days and then healed completely The possibility suggested by this history led to an autopsy at which a large thrombus was found straddling the bifurcation of the pulmonary artery Examination of the saphenous vein showed thrombus extending from the site of the scar to the point of entrance into the pulmonary vein

From the figures collected by Hamman the most important natural causes of sudden death (i e excluding cases of poisoning and trauma) are

Illustrative Case

I

(#192642 Admitted March 21 1948 Died March 29, 1948)

THIS 47 year old Negro housewife was admitted because of loss of consciousness

Her father had died of a stroke She had had an operation in 1933 with removal of a myomatous uterus and a cystic ovary Her blood pressure at that time was 200/140 During 1938 to 1940 she was followed carefully under treatment with potassium thiocyanate On one occasion she had a left hemiparesis accompanied by paresthesias

Two and one half months before the final admission she began to have episodes of non radiating precordial pain which followed exertion but occasionally appeared at rest and were accompanied by dyspnea In February 1947, she developed epigastric distress followed by vomiting of a quart of reddish fluid Following this she had anorexia with nausea and episodes of vomiting coming several times a week She occasionally had what was described as a tarry stool

Four hours before admission while sitting quietly she had a flushed feeling accompanied by severe precordial pain She became weak and fainted

PHYSICAL EXAMINATION on admission T 102 P 106 R 28 BP 220/130

The patient had recovered consciousness and appeared in no acute distress The pupils reacted well fundi showed normal discs but there was diminution in caliber of the arteries with slight arteriovenous nicking The cervical veins were not distended The thyroid was not enlarged There was dullness at the left base posteriorly The breath sounds were distant at both bases but no rales were audible Strong radial and dorsalis pedis pulsations were felt bilaterally The precordium was quiet There was slight enlargement to the left on percussion The sounds were regular and of fair quality A short systolic murmur was heard loudest at the base A_2 was accentuated and louder than P_2 The abdomen was not tender no masses or organs were made out Pelvic examination showed an ulcerated bleeding cervical mucosa Neurological examination showed weakness of the left upper extremity which was more evident distally where significant

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From the figures collected by Hamman the most important natural causes of sudden death (i e excluding cases of poisoning and trauma) are

Diseases of the coronary arteries including coronary occlusion due to syphilitic aortitis	40%
Aneurysm of the aorta	12%
Valvular heart disease	12%
Myocardial disease	8%
Cerebral hemorrhage	8%
Pulmonary embolism	5%
Pulmonary hemorrhage	5%
All other causes	10%

This analysis was made in 1934 More recent figures would probably show fewer deaths due to aneurysm and pulmonary hemorrhage and a greater percentage due to disease of the coronary arteries In any event cardiac failure is the cause of sudden death in well over half of the cases and disease of the coronary arteries is by far the most common cause of the failure The actual mechanism of the sudden failure has been proved in only a few cases in which it has been shown to coincide with the onset of ventricular fibrillation When sudden failure occurs in an individual who has previously had no cardiac symptoms one may find a surprising degree of myocardial damage On the other hand under apparently identical circumstances there may be little or no evidence of myocardial damage

Sudden death from heart failure is instantaneous more often than is death from embolism or hemorrhage An exception is death caused by a large pulmonary embolus If the embolus is not large enough to occlude the trunk of the pulmonary artery or both main branches death is generally not immediate However the presence and type of associated disease may have an important bearing on the outcome

The chief sources of emboli are thrombi in the systemic veins or in the chambers of the heart Phlebothrombosis may occur in apparently healthy individuals sometimes as the result of very minor injuries to the lower extremities or even as the result of strenuous exertion without direct trauma If emboli arise from the peripheral veins they almost always lodge in the pulmonary vessels In the rare instances of so called paradoxical embolism the embolus passes into the left side of the heart through a patent foramen ovale and may lodge in the coronary or systemic arteries It has been observed clinically that when paradoxical embolism occurs it is in many instances preceded by pulmonary embolism which by raising the pressure in the right ventricle favors the passage of the second embolus from the right to the left side of the heart The same favorable circumstances are created by other conditions which give rise to an elevated right ventricular pressure Thrombi arising from the wall of the right ven

tricle owing to their relatively small size rarely produce sudden death by pulmonary embolism On the other hand thrombi of left ventricular origin even when small may lead to sudden death by embolization of the coronary or cerebral arteries Coronary embolism may be suspected when a patient with bacterial endocarditis dies suddenly Instantaneous death from cerebral embolism is rare and the patient usually lives long enough to show evidence of injury to the brain When embolism of the systemic circulation occurs in the absence of evidence of intracardiac thrombosis and in the absence of a patent foramen ovale it may be due to the formation of thrombi over an arteriosclerotic plaque in the aorta Such emboli may be dislodged and carried into the smaller radicles of the arterial tree

Hemorrhage may produce a fatal result in three ways (1) by loss of blood (2) by the effects of pressure upon a vital organ and (3) by damage to tissue from bleeding into its substance Sudden death from hemorrhage may occur following loss of blood at any point in the body Instantaneous death from hemorrhage is nearly always due to rupture of an aneurysm or rupture of the heart Other common sources of the bleeding are pulmonary cavitation peptic ulcer and erosion of an esophageal varix Death from a dissecting aneurysm frequently results from hemorrhage into the pericardial cavity which is an example of fatal effects from hemorrhage due to pressure upon a vital organ Another example is subarachnoid hemorrhage which is a well known cause of sudden death in young and middle aged people often in association with the development of hypertension in the presence of a congenital aneurysm Cerebral hemorrhage is the most common example in which bleeding causes death by destruction of tissue

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atrophy was present The deep tendon reflexes were intact and the sensory perception seemed normal There was no disturbance in cranial nerve function

Course in the Hospital The patient s mental situation cleared quickly and on the third hospital day she was allowed up in a chair She had some pain in her left chest and along the left arm on this day but no change in blood pressure Her temperature rose steadily following admis sion reaching a maximum of 103 No cause was demonstrated On March 29 she was feeling well After dinner while sitting up in bed she suddenly died

Laboratory Data Blood serologic test for syphilis negative hemat ocrit 30 5 sedimentation rate 36 mm per hour leukocyte count 7 450 with normal differential Urine showed specific gravity 1 012 sugar nega tive albumin 1 plus microscopic examination was normal Stools were normal color guaiac test was negative Several blood cultures showed no growth Blood nonprotein nitrogen was 52 mg % sugar 112 mg / cholesterol 183 mg % bilirubin less than 0 8 mg % alkaline phosphatase 13 Bodansky units

Lumbar puncture performed on admission showed an initial pressure of 240 mm water with normal dynamics Fluid was clear with no increase in cells or protein Wassermann negative Cultures of cervix and urine revealed no pathogenic organisms

Electrocardiogram showed left axis deviation and the type of picture seen with hypertension There was no evidence of myocardial infarction

X ray examination showed increase in the transverse cardiac diameter The lungs were clear There was dilatation of the aorta

Discussion There are two obvious features which stand out (1) The patient had known hypertensive cardiovascular disease for at least 15 years prior to her final illness and (2) death when it came was sudden and unexpected The patient had no real difficulty as a result of her hypertension from 1940 to 1947 when she began to have attacks of precordial pain following exertion and accompanied by dyspnea From the description one may assume that these attacks were due to insufficiency of coronary blood flow and in the absence of any evidence of syphilis were possibly associated with coronary arteriosclerosis Then in December 1947 there was epigastric dis tress followed by the vomiting of a quart of reddish fluid After this she had vague pain and other gastrointestinal symptoms but nothing characteristic of peptic ulcer The attack of precordial pain just before admission was severe and she became weak and fainted A definite degree of anemia was present and it seems probable that the added stress caused a temporary difficulty in cerebral blood supply with loss of function in the area affected at the time of the previous hemiplegia rather than a new cerebral accident Can all of these events be ex

plained by a single disease which can logically account for sudden death?

Sudden death may occur from ventricular fibrillation and in present case it would most likely be the sequel of a coronary occlus which is a diagnosis that must be considered

Sudden death merely from loss of blood may occur after hem rhage at any point of the body the two areas to be considered h are ruptured aneurysm and peptic ulcer In a situation in which p cordial pain of a severe degree is followed by fainting one m consider intrapericardial hemorrhage from rupture of an aneury (arteriosclerotic syphilitic or dissecting)—an example of the eff of pressure upon a vital organ by hemorrhage Sudden death fr destruction of tissue by bleeding into the substance of the brain n have occurred in this case

Embolus to the bifurcation of the pulmonary artery a coron or a cerebral artery must be considered Thrombosis of a coron artery leading to occlusion has already been mentioned

Since failure of the heart action is the cause of sudden death nea three times as often as hemorrhage and embolism combined let look at this possibility first The setting of arteriosclerosis and hyp tension with previous attacks of precordial pain provides an impr sive background but there was no appreciable fall in pressure at time of admission no electrocardiographic changes and, althou coronary occlusion would be followed by fever and leukocytosis in this case, one would not expect this degree of anemia

Instantaneous death from hemorrhage is nearly always due to ru ture of an aneurysm This may occur into the gastrointestinal tr and might explain the anemia and the previous episode of proba intestinal bleeding Syphilitic aneurysms may rupture into the pe cardium and this is the final complication of dissecting aneurys in about 80 per cent of the cases There was always a negative blo serologic test for syphilis in this case and the spinal fluid Wasserma was negative There is no objective evidence other than the dila aorta and the severe hypertension to suggest dissecting aneurys and it must be a diagnosis of exclusion Bleeding from a ruptu esophageal varix or a peptic ulcer is seldom immediately fatal

The anemia may have been associated with chronic bleeding fr the eroded cervix The fever and leukocytosis could have been due internal bleeding perhaps intrapericardial or into the gastrointesti tract It is well to note however that the one stool obtained show no blood

It is important to consider pulmonary embolus when death is instantaneous Fatal pulmonary embolism is often preceded by one or more less serious embolic episodes and frequently these are not correctly diagnosed because they are followed by no objective pul monary signs There were no signs of peripheral venous thrombosis in this patient

The presence of long standing hypertension the severe nature of the attacks of precordial pain with no drop in blood pressure during the one attack observed the x ray evidence of aortic enlargement and instantaneous death lead one to believe the most likely cause was hemorrhage from an aneurysm There was no evidence of syphilis hence dissecting aneurysm is the diagnosis of choice

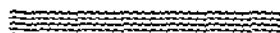
The first episode sounded like intestinal bleeding but the terminal series of events fits better with pericardial hemorrhage

ANATOMICAL DIAGNOSIS (Autopsy No 21142) History of hyperten sion Intrarenal and generalized arteriolo and arteriosclerosis Cardiac hypertrophy Idiopathic medial necrosis of aorta Two dissecting aneurysms of aorta with rupture of one Hemopericardium Encephalomalacia right thalamus Pulmonary edema and emphysema

The heart was enlarged with marked hypertrophy of the left ventricle There was only delicate intimal fat in the ascending aorta which however showed a tear extending transversely across its intima 4 cm above the aortic valve There was dissection down to the base of the heart and although the exact area of dissection through the intima was no longer visible the adventitia of the ascending aorta was roughened by clotted blood and hematoma further thickened the tissues about the pulmonary artery and ascending aorta There was rupture into the pericardial sac with a large hemopericardium The dissection upward extended only 1 cm The arch itself was delicate However in the descending aorta a hole barely 1 mm in diameter was seen in the intima 2 5 cm below the arch Beneath this was a larger oval hole through which clot protruded and adjacent to this a third slit like tear measuring 3 mm in length Behind these tears was a longitudinal bulging zone extending virtually the entire length of the descending aorta On section this was filled with firm clot which had torn through the media The tear and enclosed hematoma formed a channel through only half of the circumference of the aorta The remainder of the aortic wall was normal The dissection stopped just above the celiac axis Microscopically there was marked sclerosis of the medium sized vessels and a moderate amount of arteriosclerosis in the usual tissues

SUMMARY This 47 year old Negro woman was known to have hyper tension for fifteen years and had a left hemiparesis Ten weeks before death she developed precordial pain and dyspnea Later she had severe epigastric distress and vomited reddish fluid The day of admission pre cordial pain developed followed by unconsciousness Examination revealed hypertension dilatation of the aorta and cardiac enlargement

There was anemia and she was febrile After a period of rapid improvement she died very suddenly The long standing hypertension the severe precordial pain without hypotension or electrocardiographic changes the aortic dilatation and the instantaneous death all suggested DISSECTING ANEURYSM WITH RUPTURE INTO THE PERICARDIUM At autopsy in addition to the lesion in the ascending aorta with pericardial rupture there was an older dissection in the descending portion accounting for the attack of epigastric pain some weeks before death



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Chapter 5

FAILURE OF URINARY EXCRETION

THE CONDITIONS which fall under the general heading of this chapter include those which lead to renal insufficiency or interfere with the passage of urine from the kidney to the exterior The cause of anuria may be prerenal renal or postrenal Since the kidney is a homeostatic organ and is concerned with the control of excretion of many dissolved substances as well as water lesser grades of excretory failure may not be detected by simple measurements of urine volume Even when the volume is greater than normal the kidney may be unable to excrete adequate amounts of dissolved substances *In some cases the excretion of both water and nitrogen may be accomplished* quite satisfactorily by kidneys which are totally incapable of exercising normal control over the excretion of other substances such as electrolytes This may be due to intrinsic failure on the part of the kidney or it may occur because the dissolved substances are not presented to the kidney under appropriate chemical or physical circumstances

Table 7 presents a list of the causes of failure of urinary excretion Broadly speaking these are arranged under three headings postrenal renal and prerenal Each of the three main categories may be *encountered in either an acute or a chronic form and the tabulation* is arranged to indicate this As mentioned previously such a table should serve only as a skeleton for reviewing possible diagnoses In many cases more than one of the three principal factors may be involved and in some instances an acute factor may be superimposed upon one or more chronic factors These various combinations may produce some of the most difficult and puzzling diagnostic problems encountered in clinical practice A typical example of a complex picture is that of so-called lower nephron nephrosis in which prerenal

Table 7 Failure of Urinary Excretion

I Acute failure of urinary excretion
  A Due to postrenal factors
    1 Obstruction of urinary tract
      a Urethral stricture or calculi
      b Prostatic obstruction hypertrophy tumor or inflammation
      c *Ureteral obstruction by tumor masses inflammatory reactions calculi crystals (sulfonamide) blood clots*
    2 Bladder abnormalities tumors neurogenic malfunction trauma
    3 Obstruction of renal veins thrombosis tumor intra abdominal pressure
  B Due to renal failure
    1 Acute glomerulonephritis
    2 Acute pyelonephritis
    3 *Acute tubular necrosis due to*
      a Inorganic substances chiefly heavy metals (mercury bismuth arsenic etc)
      b Organic substances such as carbon tetrachloride sulfonamides etc
      c Intravascular liberation of hemoglobin or myoglobin (mis matched transfusions Rh incompatibility other blood incom patibilities blackwater fever distilled water irrigations during transurethral operations paroxysmal hemoglobinuria or myo globinuria)
      d *Severe injuries severe burns and shocklike states*
      e Acute hepatic insufficiency
    4 Acute bilateral cortical necrosis
  C Due to prerenal factors
    1 Circulatory failure
      a Thrombosis or embolism of renal arteries
      b *Forward heart failure due to traumatic shock hemorrhage* myocardial infarction anesthesia burns certain poisons etc
    2 Fluid and electrolyte depletion due to intractable vomiting or diarrhea *sodium deficiency (may be aggravated by mercurial diuretics)* etc
II Chronic failure of urinary excretion
  A Due to postrenal factors
    May be caused by same factors as noted in I A above but failure of urinary excretion may be gradual in onset and protracted in course
  B Due to renal failure
    1 Diffuse renal disease
      a Chronic glomerulonephritis
      b *Arteriolosclerotic nephritis (arteriolar nephrosclerosis)*
      c Periarteritis nodosa and disseminated lupus erythematosus
      d Other types often with nephrotic picture myeloma amyloid dis ease trimethadione intoxication syphilitic nephrosis intercap illary glomerulosclerosis lipoid nephrosis

2 Circumscribed renal disease
   a Sclerosis of larger intrarenal arteries
   b Chronic pyelonephritis
   c Congenital polycystic disease
   d Tuberculosis
   e *Infarction due to small emboli*

3 Miscellaneous causes
   a Vitamin D intoxication
   b Hyperparathyroidism
   c Medullary congenital cysts with salt losing effect simulating Addison s disease
   d Sarcoidosis
   e Eosinophilic granuloma

C Due to prerenal factors
   1 Circulatory failure due to partial chronic obstruction of renal arteries by thrombi arteriosclerotic plaques or tumors
   2 Fluid and electrolyte depletion due to protracted vomiting and diarrhea or inadequate intake
   3 Long term administration of alkalis

factors (shock and vomiting) may be combined with renal tubular necrosis and a postrenal obstructive factor (blockage of the excretory pathways by debris) Considered from another point of view the ultimate clinical picture of renal dysfunction results from the composite effect of disease or injury upon renal blood flow glomerular filtration tubular secretion and reabsorption and certain renal metabolic functions such as the formation of ammonia The extent to which these various functions are impaired varies from case to case in any given disease Methods have been developed for measuring quantitatively the degree of dysfunction of the various components contributing to normal renal function Interpretation of the results obtained *by these methods is open to question when the kidney is diseased* Moreover the methods are elaborate and are not generally available Therefore in the discussion which follows we shall refer only to the use of those techniques which are at the disposal of every physician either in his office or in the hospital which serves him a careful history a thorough physical examination *detailed examinations of fresh* urine specimens employing catheterized specimens when necessary simple tests of renal function and measurements of the chemical composition of the blood

ACUTE FAILURE OF URINARY EXCRETION

It is desirable to begin the study of these cases with an attempt to discover or exclude *postrenal factors* If the bladder is distended with

urine the cause of the disturbance is to be sought either in the urethra in the periurethral structures such as the prostate or in the bladder itself Rectal examination may disclose a hypertrophied prostate a tumor or a periurethral abscess It is important to remember that the median lobe of the prostate may obstruct the urethra without there being any significant general enlargement of the prostate gland If simple inspection and palpation produce only negative evidence additional information may be obtained first by catheterization of the bladder and then by urethroscopic and cystoscopic examinations When the distention of the bladder is neurogenic in origin this can best be established by cystometric studies

Acute failure of urinary excretion due to *obstruction of the outflow tract above the level of the bladder* is rare It is most likely to occur when because of congenital malformation or disease of the opposite kidney or ureter the excretory load is being carried by only one kidney Under these circumstances blockage of the one functioning ureter will of course lead to complete anuria Frequently acute obstruction of one ureter by calculus will cause transitory reflex anuria on the opposite side Both ureters may occasionally be blocked by calculi In the study of lesions situated above the level of the bladder catheterization of the ureters with examination of the urine from both sides and retrograde pyelography provide essential information Excretory pyelography may also be helpful but better definition of the structures is usually obtained by the retrograde method

Again following the precept which has been repeatedly emphasized in these pages when urinary excretion fails one should think first of postrenal factors for these offer the greatest potentialities for successful therapy The common conditions which come under this heading have been indicated in Table 7 and they will not be discussed in detail here If they are borne in mind they are usually not difficult to demonstrate Obstructions of the lower urinary tract may present themselves as *acute emergencies* when in fact they are based upon long-continued chronic disease A man with prostatic hypertrophy may have had what he considers to be only minor urinary symptoms and may be totally oblivious to nitrogen retention until the bladder suddenly decompensates and he is unable to void Similarly a bladder stone or polyp may give rise to no symptoms until it slips down into the urethra and abruptly blocks the flow of urine In the early days of *sulfonamide therapy* many cases in which the ureters were obstructed by crystals were mistaken for cases of toxic renal failure

Acute renal failure may be due to a variety of diseases and toxic

substances *Acute glomerulonephritis* in its classic form with edema hypertension albuminuria and hematuria is easily recognized The clinical picture however displays a wide spectrum In some cases there may be gross changes in the urine while edema and hypertension are negligible In other cases the urine may be normal except for slight albuminuria and slight microscopic hematuria while the hypertension may be so severe as to lead to encephalopathy and cardiac failure *Acute pyelonephritis* is frequently associated with some post renal obstructive factor Pyuria rather than hematuria is the predominant urinary abnormality Cultures of the urine usually reveal the causative organism Tenderness in the region of the kidneys bladder symptoms and fever are common manifestations

Acute tubular necrosis causes a peculiar type of failure of urinary excretion which has been recognized under a variety of descriptive terms (lower nephron nephrosis acute renal failure transfusion kidney crush syndrome toxic nephrosis hepatorenal syndrome etc) The causes of this type of renal failure vary from ingestion of nephrotoxic substances to complicated conditions in which there is frequently a prerenal factor as well as damage to the renal tubules The effect upon renal function is approximately the same regardless of the cause of the disturbance Initially there is usually a violent systemic reaction frequently accompanied by vomiting diarrhea and a transitory decline in blood pressure Following this there is a period of oliguria lasting for several days to two or three weeks At the end of the period of oliguria diuresis sets in and there may be massive excretion of dilute urine which closely resembles an unelaborated plasma filtrate The period of diuresis may be correlated with regeneration of cells in the damaged renal tubules It is always essential to make a careful search for the cause of this type of acute renal failure If due to the ingestion of a *heavy metal* such as mercuric chloride careful examination of the mouth may disclose characteristic lesions Acute tubular necrosis from mercuric chloride may also result from absorption of this salt through other channels e g the vagina when mercuric chloride has been used as an abortifacient The diagnosis of heavy metal poisoning can usually be established on the basis of historical data or by identifying the metal in the excreta or tissues *Carbon tetrachloride* may be cited as an example of the organic substances which cause acute tubular necrosis This chemical is widely used and its dangers are not always fully appreciated It may enter the body either by inhalation or via the gastrointestinal tract In many cases a history of exposure can be elicited only by direct questioning concerning the

use of cleaning fluids paint solvents fire extinguishers etc Carbon tetrachloride causes intense damage to the kidney, and anuria may be noted within a few hours of exposure There are usually other symptoms chiefly vomiting and diarrhea and with the passage of time signs of damage to the liver and central nervous system

Intravascular liberation of *hemoglobin and myoglobin* occurs under a variety of conditions of which the most frequently encountered are those listed in Table 7 In many of these conditions the intravascular liberation of hemoglobin is accompanied by a sharp generalized reaction manifested by shock fever and vomiting Acute renal failure following transfusions of incompatible blood is now well recognized A similar type of disturbance may follow hemolysis of one s own blood provided the amount of hemolysis is sufficiently great An interesting example of this type is the development of hemoglobinemia and acute renal failure following the use of distilled water or tap water for irrigation during transurethral prostatic resection Since the pressure in the irrigation system is usually about ten times that of the pressure in the pelvic veins considerable quantities of water may gain access to the blood stream through the large number of veins exposed in the urethra

During World War II a large amount of information was accumulated concerning the role of *injuries severe burns and shocklike states* in producing acute renal failure Many of the terms employed to describe the condition signified a causal relationship e g crush syndrome shock kidney traumatic uremia burn nephritis In all of these conditions the effect upon the kidney is approximately the same Lucke on the basis of his pathological studies grouped them under the heading of lower nephron nephrosis The so called hepatorenal syndrome falls into this same general category

The urinary findings in acute tubular necrosis vary with the stage of the disease Early in the period of oliguria there may be considerable amounts of protein and casts If the disturbance is due to hemoglobin or myoglobin the urine may have a deep brown coffee color and the casts may contain pigment Azotemia may appear rapidly and hyperkalemia may develop In the latter phases of oliguria the earlier hypotension may be replaced by hypertension of moderate degree In the phase of diuresis the urine has a low specific gravity may contain no detectable protein and has a low concentration of nonprotein nitrogen As the kidney recovers it regains the ability to withhold water and to concentrate dissolved substances

Bilateral cortical necrosis of the kidneys is a rare condition which

may at times be confused with pre eclamptic toxemias of pregnancy or with acute tubular necrosis It is characterized by thrombosis of the renal arteries with resulting infarction of the renal cortices It is almost always encountered in the later stages of pregnancy and is frequently associated with premature separation of the placenta This relationship is usually the key to the diagnosis

As stated above *prerenal factors* play an important role at least in initiating renal failure in cases of acute tubular necrosis Under certain conditions these factors may in themselves lead to failure of urinary excretion Thrombosis or embolism of the renal arteries is an example of this type A variety of conditions which lead to forward heart failure may cause failure of urinary excretion owing to the fact that the blood is not delivered to the kidney in sufficient volume or at a sufficiently high pressure to permit adequate renal function This type of excretory failure is reversible under appropriate circumstances In patients with congestive heart failure who have long been treated by restriction of fluid and electrolyte intake a serious form of excretory failure may be induced by superimposing vigorous treatment with mercurial diuretics

CHRONIC FAILURL OF URINARY EXCRETION

Chronic failure of urinary excretion may be caused by the same postrenal factors as noted in the previous section The same care should be exercised in searching them out for here again the therapeutic potentialities are great

The diagnostic difficulties encountered in cases of chronic renal failure are greater than those encountered in acute renal failure owing to the fact that many types of kidney disease regardless of the nature of the primary kidney involvement tend to progress toward a general failure of renal function The longer the disease has been present the more difficult does the diagnostic problem become From an anatomical point of view one may differentiate between those diseases which affect the kidneys diffusely and those which involve only circumscribed areas of renal tissue In the first group there are such diseases as chronic glomerulonephritis arteriolosclerotic nephritis amyloid disease *and intercapillary glomerulosclerosis* In the second group we have such diseases as congenital polycystic disease renal tuberculosis and chronic pyelonephritis In the strictest sense this division into two groups is not an absolute one In glomerulonephritis for example all of the glomeruli are not involved to the same extent Some of them may appear to be quite normal Furthermore it is not

uncommon to find at postmortem examination that the kidneys show a combination of two or more types of renal disease For example the effect of polycystic disease is gradually to destroy bit by bit the healthy secreting renal tissue mainly by pressure of the enlarging cysts on the surrounding kidney tissue When this disease reaches an advanced stage there remain between the cysts only narrow strands of tissue containing a few glomeruli In spite of the fact that the nonprotein nitrogen of the blood may be constantly elevated to a considerable degree these narrow strands of tissue with their functioning glomeruli and tubules are still sufficient to preserve life Death may occur only under the stress of some new infection or when vascular disease destroys the few remaining bits of secreting tissue Another example of the merging of two types of renal disease is seen in the late stages of chronic pyelonephritis This disease starts as a circumscribed type of renal lesion but with the passage of time both the clinical and pathological pictures develop many of the features of arteriolosclerotic nephritis with severe hypertension It is also well known that as chronic glomerulonephritis progresses the clinical features of nephrosis may develop and these features may eventually be superseded by those of arteriolosclerotic nephritis

The clinical manifestations of renal disease will reflect to a certain extent the difference which exists anatomically between diffuse and circumscribed renal disease Although this difference is not constant and precise enough to allow one to distinguish between the two anatomical types in all cases it does enable one to separate them clinically in a high enough percentage of cases to make the differentiation a very practical one Clinically the distinguishing features are mainly two (1) In patients with circumscribed slowly advancing disease of the kidneys there is quite frequently evidence of severe impairment of renal function without there being any symptoms of uremia Such a patient may appear well for many months or even years with a consistently elevated nonprotein nitrogen and kidneys able to excrete only a trace of phenolsulfonphthalein This is particularly true if severe hypertension does not develop In the presence of diffuse renal involvement such a marked degree of impaired renal function is almost always accompanied by severe symptoms of uremia (2) In the cases due to diffuse renal involvement the sediment of the centrifuged urine is usually abundant consisting mainly of epithelial cells red blood cells and casts whereas in cases of circumscribed disease the urinary sediment is usually slight in amount and few casts are found However should there be any large amount of sediment the cells composing it are usually pus cells

Of practical value from the viewpoint of both diagnosis and prog nosis is the level of the blood pressure It is of course a well docu mented fact that primary renal disease may induce hypertension Likewise particularly in the older age group one sees many cases in which severe renal insufficiency has been the result of hypertension with extensive involvement of the small renal vessels In the later stages when severe renal damage has taken place it may be ex tremely difficult to tell whether hypertension or renal disease was the primary factor since in both situations the picture of malignant nephrosclerosis with severe hypertension may develop Careful attention must be paid to the history and the course of the disease particularly in regard to infection the appearance of edema symp toms of hypertension previous recordings of blood pressure and urinary findings and rate of progress of the disease

If renal insufficiency is accompanied by a normal blood pressure this not only is a hopeful sign from the prognostic point of view but it also has certain diagnostic implications Patients with *subacute bacterial endocarditis* may develop a diffuse nephritis which leads to severe renal insufficiency without any elevation of blood pressure The cardinal manifestations of the endocarditis may be minimal and completely overshadowed by this course of events Uremia without hypertension may also occur in patients with *amyloid disease* pre sumably in certain instances at least because of the diffuse infiltra tion of the muscular coats of the smaller arterial vessels by the amyloid The *myeloma* kidney is a well recognized condition leading to a picture of chronic nephritis without development of an abnor mal blood pressure In such cases one may not find either hyper globulinemia or the abnormal type of protein in the urine In systemic *lupus erythematosus* the renal picture may show the char acteristics of a diffuse nephritis in the presence of azotemia and a normal blood pressure In contrast renal involvement in *periarteritis nodosa* is almost uniformly accompanied by hypertension In those rare instances in which *renal tuberculosis* is extensive enough to lead to renal insufficiency there may be no accompanying cardiovascular abnormalities

The clinical picture characterized by extensive edema rather marked albuminuria and a low serum albumin concentration has been designated generally as the nephrotic syndrome The prototype of this syndrome is the true lipoid nephrosis of children which affects the renal tubules and is so often associated with recurrent attacks of pneumococcal peritonitis In adults it is most commonly seen during the course of chronic glomerulonephritis This clinical feature may

be present in diabetic patients with the type of *intercapillary glomerulosclerosis* described by Kimmelstiel and Wilson The picture of *amyloid nephrosis* is also a well known clinical entity During the early or later stages of *syphilis renal* involvement producing this syndrome may take place and is of importance because with proper therapy the damage may be reversible Even rarer causes are renal vein thrombosis and toxicity from the administration of the anticonvulsant *trimethadione* which is currently used in the treatment of epilepsy

When failure of urinary excretion is the principal manifestation of disease the urine should be tested for excessive amounts of calcium and the blood calcium level should be determined in all cases with renal calculus Hyperparathyroidism should be suspected when the blood calcium level is elevated *Vitamin D intoxication may lead to* the development of renal insufficiency and a recent experience illustrates the importance of skillful history taking if the vital information is to be obtained *This patient* was referred because of chronic nephritis She also had mild arthritis but denied taking any vitamin D preparations During subsequent questioning the appearance of the vitamin D preparation was described to her and she immediately recognized it as medication given for the arthritis by her physician *The nature of this medication had not previously been revealed to* her Detection of the characteristic deposits of calcium in the conjunctivas and in the mucous membranes about the lips will also lead one to recognize this syndrome

In younger individuals a salt losing nephritis may result from *the pressure of small congenital cysts* in the medullary region *The* clinical picture may closely simulate that of Addison s disease but renal function tests and the failure of response to desoxycorticosterone acetate furnish the information necessary to make the distinction

Prerenal factors which are of importance in chronic failure of urinary excretion are of the same type as those operating in *acute failure* The arterial blood supply to the kidneys may gradually be obstructed by tumors thrombi or arteriosclerotic plaques Chronic fluid and electrolyte depletion may also play a role The alkalosis produced by the long-continued use of alkalis in the treatment of duodenal ulcer may cause a rise in the blood nonprotein nitrogen and a decrease in renal function with deposit of calcium in the kidneys Some patients will neglect to tell of their use of alkaline powders and the crucial information may be obtained only by direct questioning.

Illustrative Cases

I

(#136832 Admitted June 19 1952 Died July 16 1952)

THIS 60 year old white male was first admitted for a diverticulectomy of the bladder and transurethral resection in April 1952 In 1912 he had developed a urethral discharge and because of subsequent intermittent obstruction was catheterized He was found to have a positive serologic test for syphilis in 1925 and received intermittent treatment over several years In 1938 he had visual difficulty with a feeling of weakness on the right side and a tendency to stagger backward when walking He was thought to have cerebral arteriosclerosis

His admission in April 1952 was because of intermittent hematuria of ten years duration and symptoms of prostatism for nine months He was reported to have had hypertension for two months but the blood pressure was 120/80 There was evidence of loss of weight the spleen was palpable and a large mass was felt in the lower mid abdomen The nonprotein nitrogen was 32 mg % The urine was grossly bloody The hematocrit was 30 Various findings made during the first admission and until death are listed in Table 8 Gastrointestinal series showed a small hiatus hernia and prominent rugal folds in the duodenal bulb Barium enema revealed no abnormality Intravenous pyelogram demonstrated tortuous ureters but the kidney architecture seemed normal There was a huge bladder diverticulum X ray of the chest was normal Urine culture grew out a staphylococcus aureus On April 14 a suprapubic diverticulectomy was performed and two weeks later a transurethral resection His urine output remained good He received transfusions on April 14 25 26 and 27 The hematocrit on discharge was 35 On May 22 the urine contained 50–70 white cells per high power field and he was started on a sulfonamide 4 gm daily

When the patient was seen June 3 16 days prior to the second admission the urine contained only a few white blood cells and there was 75 ml of residual urine The sulfonamide was continued Two days later he complained of weakness and after another two days of urinary retention he developed headaches dyspnea and edema The blood pressure was 160/120 Moist rales were noted at the lung bases and the liver was palpated 4 cm below the costal margin There was edema of the legs and he was pale The urine showed 1 plus albumin and a few leukocytes The chest

x ray showed some obliteration of the costophrenic angles The sulfonamide was continued and he was digitalized Eight days before entry his blood pressure was 200/110 He appeared cachectic and walked with difficulty presumably because of generalized weakness The heart was not enlarged and no murmurs were heard There was ankle edema The urine was free of albumin and casts but contained 10 white and 50 red cells per high power field Nonprotein nitrogen was 130 mg % with phosphorus 12 mg % and hematocrit 28 The next day the patient voided 200 ml of

Table 8

DATE	B P	URINE	NPN	Na	K	Cl	P	HT
4/6	120/80	grossly bloody						
4/7		gross hematuria	40	134	5	105	3 8	30
4/17			32	127	3 9	99	2 8	
4/30			44					35
5/22		50–70 wbc						
6/3		10 wbc						
6/7	160/120	1+ alb						
		5 wbc						32
6/11	200/110	10 wbc	130				12 2	28
		50 rbc						
6/19	140/90	1+ alb	162					
		loaded rbc						
		occ wbc						
6/20	206/110		220	143	10 2	113	14 6	27
6/23			178	128	4 6	103	7 4	
6/26	190/90	alb 3+	162	119	4 2	89	6 6	22
		3 wbc						
		75 rbc						
7/1			160	103	4 6	76	7 2	
7/8			100	140	5 3	116	1 9	19
7/11			69	144	5 0	117	1 8	
7/14		alb 2+	80	147	7 2	127	2 0	
		wbc clumps						
		3 rbc						
		occ gran cast						

Urine specific gravity ranged from 1 005 to 1 010

clear urine On June 19 he reappeared a few hours after onset of uncontrollable shaking movements of the head and shoulders The blood pressure was 140/90 and there were episodic shaking movements of the head and arms The urine contained albumin and was loaded with red cells Nonprotein nitrogen was 162 mg % He complained of headache felt weak and became incontinent His level of consciousness slowly declined and he became semicomatose There was a story of difficulties at home which led to suspicion that he had ingested some poisonous substance

PHYSICAL EXAMINATION on second admission T 98 6 P 76 R 16 B P 206/110

The patient responded poorly was pale and showed evidence of loss of

weight The retinal arteries were narrowed and there was arteriovenous compression Coarse rhonchi were heard The heart was not enlarged There was an apical systolic murmur The liver spleen and kidneys were not palpable The pulses were equal and symmetrical and no localizing neurological signs were detected

COURSE IN THE HOSPITAL The urine output was reasonably good varying from 1 000 to 3 000 ml during the 1st week 800 to 2200 during the 2nd 900 to 2800 the 3rd and 500 to 2700 the final week Culture showed a staphylococcus albus He had no fever until the 3rd week when the temperature reached 102° and persisted above normal during the final week On admission the leukocyte count was 8 300 with 4% eosinophils There was apparent improvement in renal function with gradual decrease in the nonprotein nitrogen and return of phosphorus to normal levels During this period there was difficulty because of low serum sodium and chloride which was largely corrected by dietary measures There was per sistent distention of the abdomen The patient remained in a semicomatose state and developed signs of pneumonitis

On July 13th he seemed to be improving but two days later his coma deepened and the signs of consolidation increased despite antibiotic therapy On the day of death he had two diarrheal stools and vomited dark blood

LABORATORY DATA Blood pressure readings urine examinations and certain of the blood chemical findings during the period of observation are presented in Table 8 Blood serologic test for syphilis was negative On June 20 acid phosphatase was 3 4 units alkaline phosphatase 4 4 Bodansky units CO_2 9 mEq /L albumin 4 8 gm % globulin 3 5 gm / calcium 10 mg % spinal fluid sugar 76 mg / chlorides (spinal fluid) 148 mEq Spinal fluid Wassermann was negative protein 43 mg % cell count 4 Venous pressure was 60 mm of glucose

Electrocardiogram on June 11 showed normal rhythm QRS complex prolonged right bundle branch block On June 20 T waves were more peaked with persistence of right bundle branch block

DISCUSSION The most important feature of this case was the rapid development of a severe degree of renal insufficiency without any clear cut story of a period of marked oliguria or anuria Accom panying the azotemia there was considerable elevation of blood pres sure The urinary findings were variable but were noteworthy for low specific gravity slight to moderate amounts of albumin and white cells and red cells in moderate numbers without significant numbers of casts In the hospital his nonprotein nitrogen fell to lower levels and the elevated phosphorus returned to normal In spite of this chemical improvement there was no corresponding improvement in the physical status He developed signs of pulmonary consolida tion had diarrheal stools and vomited blood

There are many situations in which there may be sudden appear

ance of renal insufficiency with uremia Those which must be con sidered in this case may be listed as follows

(1) Urinary tract obstruction of some type
  (a) in the urethra,
  (b) in the prostate
  (c) a pelvic mass possibly due to syphilis or postoperative complications
  (d) sulfonamide precipitation
(2) Acute glomerulonephritis
(3) Heavy metal poisoning (mercury or some other nephrotoxic substance)
(4) Lower nephron nephrosis
  (a) secondary to irrigation during the prostatic operation
  (b) due to sulfonamides
(5) Periarteritis nodosa
  (a) acquired
  (b) spontaneous
(6) Congenital medullary cysts leading to diminished ability to re tain salt plus infection as a precipitating factor
(7) Various other conditions in which uremia may develop such as bacterial endocarditis eosinophilic granuloma, myeloma tosis amyloidosis Addison s disease

In view of the operative procedures performed one of the impor tant possibilities to exclude is obstruction of the lower urinary tract Catheterization revealed no obstruction of the urethra and there was no evident residual urine or evidence of prostatic obstruction during the postoperative period No pelvic mass was felt during the final admission and it seems unlikely that uremia would develop owing to a bilateral ureteral obstruction unless there had been some reac tion around the operative site with hemorrhage which is unlikely in view of the good urinary output which the patient maintained The elevated acid phosphatase is supposedly pathognomonic of prostatic carcinoma

It would seem unlikely that he had a simple acute glomerulo nephritis The findings in the urinary sediment were variable The amount of albumin was never large except toward the terminal phase The blood pressure was high before nitrogen retention was well developed There was no story suggestive of the onset of glo merulonephritis Poisoning by mercury is usually associated with much more evident changes in the urinary findings including the presence

of sugar The gastrointestinal symptoms in severe poisoning would be more marked and one would expect a history of more evident suppression of urine flow Rarely is hypertension of this degree seen in acute mercury poisoning

The tendency toward improvement with lowering of the nonprotein nitrogen during the later phases of the illness suggests the possibility of lower nephron nephrosis during the diuretic phase However during the initial stages of this disorder there is almost always evidence of reduced urine flow Moreover there is usually a preceding event that clearly alters the circulation to the kidney or a story of some severe injury hemolysis crushing burns etc A mannitol solution was used to irrigate the field during the operation and there was no evidence suggesting a hemolytic reaction Acute tubular necrosis may occur as a result of sulfonamide administration but again there was no evidence suggesting a sudden or severe reaction or period of shock Nevertheless the possibility of lower nephron nephrosis cannot be easily excluded in view of the evidence of improvement in renal function

There were certain indications that the patient was ill with some undiagnosed condition at the time of the first admission The spleen was thought to be palpable and the hematocrit was low although one cannot be certain that this was not due to chronic blood loss from the recurrent hematuria The hypertension the accumulation of fluid in the pleural cavities in the absence of heart failure the weakness with difficulty in walking the bowel difficulties during the latter stage of the illness and the vomiting of blood terminally all suggest the possibility of periarteritis nodosa

There was evidence that sodium was being excreted at an excessive rate This brings several possibilities to mind such as small renal medullary cysts resulting in the salt losing type of renal defect simulating Addison s disease Some trigger mechanism such as an infection may be necessary to bring this defect to the stage of overt impairment of renal function with nitrogen retention It seems unlikely that such a situation would be accompanied by such marked hypertension and certainly this could not be a case of Addison s disease

From examination of the fundi it was evident that the patient had arteriosclerosis and one would wonder whether there was an underlying sclerosis and partial occlusion of the renal arteries and whether the patient was on the verge of renal insufficiency at the time of his operation Conceivably renal failure might have been provoked by

either a small added element of obstruction by infection or by the effects of the sulfonamide This seems a rather complex explanation and there is little evidence to support it

Finally one must consider several other possibilities that seem remote One is bacterial endocarditis in which when renal failure develops there is rarely elevation of blood pressure Eosinophilic granuloma must be thought of when a bizarre picture presents itself with evidence of renal involvement but any granulomatous masses should have been noted at operation I do not believe that one can seriously consider multiple myeloma as such rapid development of renal insufficiency would not take place The same can be said for amyloidosis Occasionally one may see gummatous lesions in the pelvis which result in ureteral obstruction Again this seems highly unlikely

The three outstanding possibilities are (1) carcinoma of the prostate with obstruction (2) lower nephron nephrosis possibly due to the sulfonamide and (3) periarteritis nodosa either spontaneous or possibly due to the sulfonamide The first seems the least likely for reasons cited above Diagnoses 2 and 3 are not mutually exclusive since there may have been renal damage by as well as an allergic reaction to the sulfonamide Because of the lack of any sustained oliguria and the high blood pressure I do not believe that lower nephron nephrosis alone was present I think the lesions of periarteritis nodosa will be found The pulmonary lesions could be explained on that basis or they might have been due to pulmonary embolism or a type of pneumonia resistant to antibiotic therapy

ANATOMICAL DIAGNOSIS (Autopsy No 23770) History of sulfonamide therapy and multiple blood transfusions History of acute uremia with sodium loss History of bladder diverticulectomy Hydroureter and hydronephrosis Chronic cystitis and pyelitis Peripelvic abscesses Healing lower nephron nephrosis Thrombi renal veins Intrarenal arteriosclerosis Organizing lobular pneumonia Microscopic pulmonary abscesses (gram positive cocci) Thrombi in minute pulmonary vessels Focal necroses basal ganglia and cerebral cortex Chronic prostatitis Microscopic prostatic abscess (gram negative rods) Acute ulceration esophagus and duodenum Chromophobe adenoma pituitary Hyperplastic femoral bone marrow

The fundus of the bladder wall was thick and the mucosa reddened What remained of the prostate showed nodularity and scarring Both ureters were dilated and thin The kidneys were equal in size and pale yellow in color The cortico-medullary markings were almost completely obscured Microscopically the kidneys were of interest in that they showed interstitial scarring and infiltration There was also evidence of regeneration of the epithelium which gave the tubules an atrophic appearance

This change was interpreted as having resulted from earlier necrosis of the epithelium as a consequence of lower nephron nephrosis The glomeruli showed relatively little change and there was no evidence of any type of progressive glomerulonephritis There were some sclerotic arterioles and arteries but this change was not extensive

SUMMARY This 60 year old man who gave a history of hematuria for 10 years entered the hospital for removal of a bladder diverticulum and for prostatectomy because of benign hypertrophy Postoperatively he was placed on a sulfonamide because of a urinary tract obstruction following which he developed hypertension and uremia There was no definite history of oliguria and the urinary output remained good in the few weeks before death Despite apparent improvement in renal function he grew worse and died after developing signs of pulmonary consolidation The three diagno tic possibilities considered were carcinoma of the prostate acute tubular necrosis due to the sulfonamide and periarteritis nodosa At autopsy there was some intrarenal arteriosclerosis and a chronic cystitis and pyelitis Microscopically the kidneys showed interstitial scarring and infiltration as well as evidence of subsiding ACUTE TUBULAR NECROSIS It is possible that this was due to the sulfonamide

II

(#191017 Admitted Dec 30 1947 Died Jan 15 1948)

THIS 45 year old white female entered because of puffiness of the face of two days duration and inability to pass urine and diarrhea for 24 hours

Her father had had hypertension with a cerebral hemorrhage and a sister had died eleven years previously of tuberculosis The patient had had marked scoliosis and kyphosis since early childhood She had scarlet fever at age 15

On December 8 she developed chilly sensations and signs of an upper respiratory infection The following day she had a shaking chill with a temperature of 103 Her throat was sore and she had difficulty in swallowing After five days of treatment by her local physician she ceased taking the sulfonamide pills For the next two weeks she had a slight headache and some listlessness On December 25 she noted fluttering of the heart and felt very ill Four days later her eyelids were puffy and her hands and ankles swollen Her urine was dark and smoky in color The day before admission she developed nausea and diarrhea

PHYSICAL EXAMINATION on admission T 99 P 80 R 20 BP 160/100

The patient was acutely ill The pupils were irregular but reacted normally There was retinal edema but no hemorrhages or exudates The arteries were narrow in appearance The pharynx was hyperemic There was no lymph node enlargement The cervical veins were not distended The heart was difficult to outline because of the marked deformity of the chest No murmurs or friction rubs were heard The peripheral vessels were soft to palpation The liver was palpated 2 fingerbreadths below the costal margin There was no costovertebral angle tenderness and no edema Neurological examination showed no abnormalities

COURSE IN THE HOSPITAL The patient was put on a low salt low protein diet and was placed on penicillin 50 000 units every 3 hours The urinary output remained low and the blood pressure rose to 200/100 After a few days she developed ecchymoses on the buttocks No abnormality was noted in bleeding time clotting time or platelet count She had persistent tachycardia and a temperature elevation to 100 until 2 days before death when it reached 103 She was apprehensive grew more drowsy and was found dead on January 15

LABORATORY DATA Blood serologic test for syphilis was negative red blood cells 3 96 million hemoglobin 12 3 gm leukocyte count was 8 640 with normal differential during course of the illness leukocyte count rose to 22 600 Specific gravity of the urine was 1 020 albumin 4 plus

sediment 4 plus microscopic examination showed 5 to 20 red cells 8 white cells and 1 to 2 granular casts She continued to have albumin and numerous red cells in the urine Blood nonprotein nitrogen was 86 mg / (did not increase before death) calcium 9 3 mg % phosphorus 5 3 mg % total serum protein 6 1 gm % with 3 3 gm % albumin No sulfadiazine was found in the blood Phenolsulfonphthalein excretion at the time of admission was 5% at the end of two hours on January 6 it was 35% at the end of two hours Tuberculin test second strength PPD 1 plus Throat culture showed alpha streptococci Urine culture showed A aerogenes Venous pressure 65 mm of saline Electrocardiogram showed a normal record with a ventricular rate of 85 a later record showed sinus tachycardia and a rate of 130

DISCUSSION This patient obviously had some type of renal disease with uremia The essential facts are as follows

(1) Developed deformity of the back at age 3—probably Pott s disease (2) Developed an upper respiratory infection and took a sulfonamide for five days (3) Two weeks later she developed edema and passed dark brown urine (4) Blood pressure was elevated and she noted fluttering of the heart (5) Urine showed specific gravity of 1 020 and 4 plus albumin Sediment contained white cells red cells and granular casts Culture showed A aerogenes (6) Mild anemia later leukocytosis (7) Phenolsulfonphthalein excretion greatly reduced nonprotein nitrogen elevated but never over 90 mg % (8) Urine remained unchanged (9) She showed progressive drowsiness

The first problem to be considered is the nature of the renal disease Certain practical criteria to separate the two major types of renal disease have been outlined and their application to this case would make it appear that there was a diffuse type of renal involvement Therefore the possibilities are

(1) glomerular nephritis (2) arteriolosclerotic nephritis (3) amyloid disease (4) sulfonamide nephritis and (5) periarteritis nodosa

There are many features which point to the diagnosis of acute glomerular nephritis There was an upper respiratory infection with sore throat followed after a three week interval by the sudden appearance of edema and dark smoky urine The physical findings with edema and hypertension as well as the results of urine examination were consistent with this diagnosis However the uremia seemed to remain stationary while the patient was apprehensive and had certain evidence of cardiac involvement as well as fever and leukocytosis

There was little here to suggest arteriolosclerosis The retinas showed no extensive arteriolar changes The blood pressure was never

very high There were no hemorrhages or exudates and the course seems too rapid

The Pott s disease with the possibility of long standing tuberculosis suggests that she may have had amyloid disease This could certainly not account for the acute illness It is unusual except in very advanced and long standing amyloidosis to get enough renal damage to result in hypertension and uremia

There was no trace of sulfonamide in the blood at the time of admission and it seems unlikely that this drug could have been responsible for the picture unless the lesions of periarteritis nodosa had developed This might explain the cardiac manifestations and the fever and leukocytosis as well as the renal lesion suggesting glomerulonephritis

In spite of the finding of A aerogenes in the urine the evidence does not point to a urinary tract infection as playing any major role in her illness Likewise although renal tuberculosis might be present it could not possibly explain the entire renal picture

The best diagnosis seems to be periarteritis nodosa of the secondary type due to a hypersensitivity reaction to the sulfonamide administered

ANATOMICAL DIAGNOSIS (Autopsy No 21016) History of septic sore throat with sulfonamide treatment Periarteritis nodosa with necrosis involving heart and kidney Acute glomerulonephritis Acute interstitial myocarditis with marked eosinophilic infiltration History of hypertension Kyphoscoliosis Cardiac hypertrophy right and left ventricle Chronic passive congestion liver spleen and lungs Patchy pulmonary edema and atelectasis Acute splenic tumor Spotty aplasia vertebral bone marrow

There were extensive lesions in the heart with numerous necrotic small arteries and in some areas eosinophilic infiltration The next most affected site was the kidney where there were marked glomerular changes consisting of increased cellularity and beginning hyalinization and crescent formation In addition the tubules contained blood and casts The vascular lesions in the kidney parenchyma were not conspicuous However in the pelves there were numerous necrotic arteries of the same caliber as those involved in the heart In this case there was extensive cardiac damage and this coupled with the apparent decrease in pulmonary function as a result of the chest deformity and in association with the severe renal disease apparently led to the fatal outcome The question arises as to whether all of the changes may be explained on the basis of a hypersensitivity reaction to sulfonamide or how much of the renal damage may be due to infection which was treated by sulfonamide The renal changes were certainly characteristic of those that are found associated with infections and there were relatively few damaged arteries in the cortex of the kidneys Most of the vessels that were involved in the kidneys were found about the pelves

SUMMARY This 45 year old white female had Pott s disease at the age of 3 Five weeks before death she developed a fever and sore throat taking a sulfonamide for 5 days Two weeks later she developed edema and dark urine She had fever and later leukocytosis There was reduced renal function with azotemia hypertension albuminuria and red cells and casts in the sediment The findings were indicative of a diffuse type of renal involvement and the major possibilities were glomerulonephritis sulfonamide nephritis and periarteritis nodosa Because of the fever leukocytosis cardiac manifestations and renal changes the latter diagnosis was made The heart lesions were due to PERIARTERITIS NODOSA probably resulting from sulfonamide hypersensitivity but the renal picture was that of GLOMERULONEPHRITIS of the type seen commonly after infection

portions of the kidney are slowly destroyed by inflammation leaving other portions relatively unaffected This gradual reduction in the amount of comparatively normal tissue sooner or later leads to restriction of kidney function as if portions of the kidney were being slowly amputated When this reaches a critical stage advanced renal insufficiency with uremia supervenes Hypertension of high degree appears in at least half the cases The course may be practically symptomless or characterized by attacks of pyuria accompanied by lumbar pain with or without fever In about half of the cases that come to autopsy arteriolar disease is also present These patients rarely have edema unless cardiac failure appears The specific gravity of the urine is constantly low amounts of albumin are small casts rare and red cells scarce

The clinical picture of *arteriolar nephrosclerosis* is dominated by the various manifestations of hypertension For months or years depending on the rate of evolution of the disease the urine may show no abnormalities If cardiac or cerebral complications do not first terminate the disease albuminuria and cylindruria of varying degrees appear and the clinical picture seen in advanced glomerulonephritis makes its appearance Observations made early in the course of the disease may give the only clue as to whether the patient with advanced nephritis is suffering from arteriolar nephrosclerosis or chronic glomerulonephritis History of an acute infection or of edema may give the clue to the latter diagnosis The order of magnitude of the hypertension in 1942 compared with the scant urinary findings and normal excretion of phenolsulfonphthalein make the diagnosis of primary hypertensive disease very plausible This could conceivably be the result of arteriosclerosis of one or both renal arteries but this would be unusual at such an early age

Cases of *abdominal aneurysm with involvement of renal vessels* have been reported In view of the fact that there is no positive evidence in its favor no real consideration can be given to this possibility

This woman had no symptoms referable to renal insufficiency until a few days before the final admission Pain in the left upper quadrant and flank without spasm was prominent and may have been associated with an acute pyelitis with obstruction This would account for the sudden progress of the uremia the fever pain, and mild leukocytosis No urine culture was reported

Other possibilities must be considered Although the pain did not show the distribution typical of that in acute pancreatitis this possibility must be considered Acute pancreatic necrosis may develop

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III

(#371837 Admitted March 26 1946 Died April 3, 1946)

THIS 30 year old Negro female complained of drowsiness abdominal pain anorexia nausea and vomiting of three days duration She had a long record of treatment extending back to 1929 when she had pelvic inflammatory disease and secondary syphilis The blood pressure at that time was 110/65 She was treated adequately for her syphilis In 1933 her blood pressure was found to be 125/80 Urine examination showed specific gravity 1 008 no albumin occasional hyaline casts no white cells or red cells

She returned in 1942 complaining of dyspnea on exertion and at night for five months The heart was normal in size no murmurs were audible but the blood pressure was 210/130 There was no thickening of the peripheral vessels Urinalysis showed specific gravity 1 002 no albumin rare epithelial and pus cells in the centrifuged specimen Phenolsulfonphthalein test showed 37/ excretion in fifteen minutes 58% excretion in two hours

The patient was seen again on May 8 1944 Urine examination was normal She complained of pain in the left lower quadrant and a flat plate of the abdomen showed no calculus

She was hospitalized December 30 1945 because of injuries Her blood pressure was 180/110 The heart was enlarged to the left but no murmurs were heard Urine contained albumin but no red cells or casts were noted There was a marked anemia (hemoglobin 6 gm) which could not be accounted for by bleeding from the injuries

One week before the final admission her appetite decreased she became drowsy and vomited on several occasions She had frequency of urination but the total output decreased She developed a severe aching pain which she described as starting in the epigastric region and radiating into the left upper quadrant and then into the left flank She felt chilly but had no fever

PHYSICAL EXAMINATION on admission T 100 P 100 R 22 B P 230/140

The patient was pale dehydrated and appeared drowsy but was apparently hyperesthetic and cried out when touched Arteries of the retina showed sclerotic changes and there were patches of white exudate The lungs were clear The heart was enlarged to the left but there were no murmurs The abdomen was soft but there was marked tenderness in the left upper quadrant the epigastric region and left flank There was moderate tenderness in the left costovertebral angle The liver and spleen could not be felt Rectal examination was normal

COURSE IN THE HOSPITAL She ran a low grade fever continued to feel nauseated and vomited profusely The pain in the left upper quadrant persisted On the second hospital day she developed signs of pneumonitis at both lung bases which was confirmed by x ray and penicillin therapy was begun The pneumonitis was clearing at the time of death Because of anemia she was given several transfusions The nonprotein nitrogen level gradually rose It was thought she was improving when she was found dead in bed

LABORATORY DATA Blood serologic test for syphilis was positive titer 2 units red blood cells 2 6 million hemoglobin 6 9 gm leukocytes 10 450 with normal differential Urine showed albumin 3 plus with numerous red cells and white cells few hyaline casts Blood nonprotein nitrogen was 71 mg % on admission 117 mg / at the time of death total protein 7 gm with normal albumin/globulin ratio serum amylase was 390 mg % reducing substance on first examination later 700 and fell to 540 just before death X ray examinations on March 27 showed heart and aorta normal lungs clear

Flat plate of abdomen showed no stones Portable x ray of the chest on April 3 showed the right lung clear and slight hazing at the left base Electrocardiogram showed normal sinus rhythm left axis deviation T waves normal

DISCUSSION It seems clear that this patient had some type of chronic nephritis which led to uremia The problem is to decide the nature of the renal lesion and to account for the severe upper abdominal pain during the terminal illness and the cause of her sudden death

As early as 1942 hypertension was well developed but little change was found in the urine and 37% of the phenolsulfonphthalein was excreted in 15 minutes This suggests that the patient had either essential hypertension or some circumscribed renal lesion for which four main possibilities exist pyelonephritis polycystic disease localized arterial disease or in view of the history of syphilis abdominal aortic aneurysm with involvement of the renal artery It must be added that during later examinations the urinary sediment suggested the presence of diffuse renal disease and this course of events may be of importance

Polycystic disease seems unlikely Patients with this disease either die very early or not until the age of 40 to 50 In a large percentage of the cases one or another kidney can be palpated or an enlarged shadow seen in the flat films of the abdomen

Contracted kidneys due to *chronic pyelonephritis* occur in young adults who may not have evidence of chronic cystitis or of gross urinary tract obstruction During progress of the disease irregular

portions of the kidney are slowly destroyed by inflammation leaving other portions relatively unaffected This gradual reduction in the amount of comparatively normal tissue sooner or later leads to restriction of kidney function as if portions of the kidney were being slowly amputated When this reaches a critical stage advanced renal insufficiency with uremia supervenes Hypertension of high degree appears in at least half the cases The course may be practically symptomless or characterized by attacks of pyuria accompanied by lumbar pain with or without fever In about half of the cases that come to autopsy arteriolar disease is also present These patients rarely have edema unless cardiac failure appears The specific gravity of the urine is constantly low amounts of albumin are small casts rare and red cells scarce

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behind a soft abdomen as was the case here the degree of pain was consistent but the severe collapse seen in acute hemorrhagic pancreatitis was not present and in pancreatitis pain is usually out of all proportion to the degree of tenderness The serum amylase was elevated to a moderate degree but this is not an uncommon finding in patients with this degree of renal insufficiency It is unlikely that any acute disease of the pancreas was present

With severe hypertension and symptoms referable to the left upper quadrant the possible presence of pheochromocytoma must be brought up The hypertension did not fluctuate greatly and no paroxysms were present These facts in no way eliminate the possibility but this diagnosis seems improbable

There are numerous other possibilities that could be considered—localized perforation of the gastrointestinal tract might have occurred with a walled off abscess Anemia is a frequent finding in patients with such a condition However this seems altogether unlikely

In summary the most likely diagnoses are

(1) arteriolar nephrosclerosis
(2) pyelonephritis with acute exacerbation of the infection in the kidney The cause of the sudden death might well have been a pulmonary embolus

Anatomical Diagnosis (Autopsy No 19870) Arteriosclerosis of aorta with narrowing of mouth of left renal artery Arteriosclerotic and arteriolonecrotic nephritis History of hypertension and uremia Hypertrophy and dilatation of left ventricle slight Generalized arteriolosclerosis Periarteritis nodosa of stomach and duodenum Superficial ulceration of stomach mucosa and acute and chronic inflammation with eosinophilic infiltration of stomach wall Superficial ulceration of duodenal mucosa with chronic inflammation of duodenal wall Pulmonary edema Lobular pneumonia slight Cortical adenoma of adrenal History of pelvic operation surgical absence of ovaries and tubes

Heart was enlarged Myocardium was very pale and showed a yellowish mottling suggesting infiltration with fat Coronaries were delicate There was some intimal fat in a few plaques throughout the aorta The left renal orifice was encroached upon by an arteriosclerotic plaque which narrowed it to a crescentic slit The left kidney seemed smaller than the right with a definite irregularity and depression near its upper pole On section the cortex was especially narrow at the area of gross distortion but elsewhere too the striae were indistinct and blurred The right kidney showed no gross irregularity Its cut surface showed numerous punctate hemorrhages clearly visible in several pyramids

Microscopic study showed a very extensive arteriosclerotic and arteriolosclerotic nephritis There was great narrowing of many of the moderate sized vessels in the kidney with associated atrophy and there was wide

spread arteriolosclerosis Hyalinized arterioles were seen entering the glo meruli which showed the characteristic resulting alterations In the sub mucosa of the stomach there were definite lesions of periarteritis nodosa with necrosis of the arterial wall and surrounding mononuclear and eosinophilic cells

SUMMARY This 30 year old Negro female was found to have severe hypertension with normal renal function four years before death Three years later hypertension was again noted as well as albuminuria and anemia Two weeks before death vomiting drowsiness oliguria and severe pain in the left upper quadrant and flank developed Examination revealed hypertension pallor drowsiness vascular retinitis and upper abdominal tenderness There was anemia azotemia albuminuria hematuria and elevation of serum amylase activity The early finding of severe hyperten sion before impairment of urinary function led to a diagnosis of arteriolo sclerotic nephritis The pain was thought to result from a superimposed urinary tract infection on the left Autopsy revealed extensive ARTERIO SCLEROTIC AND ARTERIOLOSCLEROTIC NEPHRITIS and periarteritis no dosa localized to the stomach and duodenum as explanation for the pain

IV

(#435440 Admitted Sept 14 1947 Died Sept 30 1947)

THIS 61 year old white female was admitted because of failing vision Her father died at age 55 of Bright s disease She had had four pregnancies all terminating in spontaneous abortion There was no history of acute nephritis

For one year she had slight puffiness of the eyelids in the morning and urinary frequency Three months before admission she noticed fatigability and saw spots before her left eye Her doctor found a hemorrhage in the eye anemia and hypertension She was treated for anemia without improvement Her vision grew worse Two weeks before admission she developed nausea and vomiting after meals

PHYSICAL EXAMINATION on admission T 98 P 72 R 20 B P 260/130

The patient appeared chronically ill The skin was loose and sallow The mucous membranes were pale Visual acuity was greatly impaired There were bilateral vitreous opacities both optic discs were blurred and there was a compact star figure in the right macular region Numerous hemor rhages and small exudates were noted in each retina There was marked retinal arteriosclerosis with narrowing of the vessels The heart was en larged to the left There was thickening of the peripheral vessels The lungs were clear A slightly tender mass was noted in the right upper quadrant which descended well with respiration There was no edema Neurological examination was normal

COURSE IN THE HOSPITAL The patient lived only two weeks after admission Her pulse rate and temperature were normal She continued to have a marked hypertension She vomited frequently and there was some edema about the eyes and slight edema of the legs Before death she had numerous convulsions Daily urine volume varied from 450 to 1200 ml

LABORATORY DATA Red blood cells 2 38 million hemoglobin 6 3 gm leukocytes 9 000 with normal differential Urine showed specific gravity of 1 006 albumin 1 plus occasional granular cast no white or red cells Blood serologic test for syphilis was negative Phenolsulfonphtha lein excretion 120 minutes trace Blood nonprotein nitrogen 106 mg / on admission rose to 181 day before death CO_2 22 5 mEq chloride 81 2 mEq serum albumin 4 4 gm / globulin 2 1 gm / cholesterol 245 mg / calcium 10 mg / phosphorus 9 1 mg / Portable x ray of the abdomen demonstrated nothing grossly abnormal

DISCUSSION It seems evident that this patient died in uremia

which developed insidiously as a result of slowly progressive renal insufficiency There was severe hypertension and severe vascular retinitis produced the earliest of the symptoms The problem is to determine the nature of the renal lesion

This patient had little discomfort until three months before admission when visual difficulties became noticeable She had been vomiting for only a short while there was advanced renal insufficiency with marked azotemia and one gains the impression that the development of uremia was a gradually progressive event taking place over a long period of time

The urine was of low specific gravity and low albumin content and contained practically no cellular elements or casts This was the state of affairs even in the presence of a very severe hypertension Thus both criteria (insidious renal failure and minimum urinary sediment) have been fulfilled for attributing this patient's illness to one of the circumscribed types of renal disease Arteriolar nephrosclerosis or chronic glomerulonephritis as the primary disease seems unlikely and one may turn for further discussion to arteriosclerotic disease, chronic pyelonephritis and congenital polycystic kidneys

One would gather that hypertension came on rather late in the course of events as there were never any symptoms referable to it or to its potential effects on cardiac function This coupled with the extreme degree of renal dysfunction makes it difficult to believe that arteriosclerosis of the renal vessels alone could have produced this picture

Contracted kidneys due to chronic pyelonephritis usually occur in young adults who may not have obvious evidence of chronic cystitis or gross urinary tract obstruction Renal function is gradually reduced as portions of the kidney are slowly amputated When this reaches a critical stage advanced renal insufficiency with uremia supervenes Hypertension of high degree may appear and the course may be relatively symptomless About 50 per cent of the patients seen at autopsy have arteriolar disease as well The urine shows low specific gravity and small amounts of albumin as in this case No urine culture was done in the present case The age of the patient is against this diagnosis and there was no history suggesting urinary tract infection in the past This diagnosis is hard to eliminate and the palpable mass in the kidney region would have to be explained as a perinephric abscess

Polycystic disease seems unlikely at first glance as such patients usually die very early in life or around the age of 40 However there

was a death from polycystic disease in a 61 year old man shown at one of these conferences last year The vascular lesions of arterio sclerosis especially in the cerebral vessels are frequently seen in patients dying of this condition Symptoms depend on the degree of cystic involvement of the kidneys and renal insufficiency may not appear until vascular disease has developed and contributed further to the renal impairment The presenting symptoms usually suggest a chronic nephritis but the urine specific gravity is low albumin excretion scant and casts are only occasionally seen Manifestations due to arteriosclerosis are commonly seen such as headache dizziness blurring of vision Most of the cases show a well marked hypertension and in about half of them a mass which descends with respiration is felt in one or both kidney areas

Therefore since the clinical picture suggests a circumscribed type of renal damage with slow progress into uremia urine of low specific gravity small amounts of albumin and few casts despite marked hypertension and a palpable mass in the region of the right kidney the likely diagnosis is

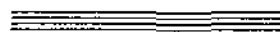
Congenital polycystic disease of the kidneys generalized arterio sclerosis with involvement of the renal arteries tipping the scale toward a degree of renal insufficiency incompatible with life

Anatomical Diagnosis (Autopsy No 20822) History of hypertension and uremia Congenital polycystic kidneys Marked general and intrarenal arteriosclerosis and narrowing of orifices of renal arteries Arteriosclerotic and arteriolosclerotic nephritis Generalized severe arteriolosclerosis Organized thrombi small vessels of pancreas heart and brain Focal myocardial scarring Focal encephalomalacia with hemosiderin pons and cerebral cortex History of cardiac failure Cardiac hypertrophy Hydropericardium Pulmonary edema Sacral and leg edema Chronic passive congestion of pancreas and liver Hemosiderin spleen Pituitary chromophobe adenoma Colloid adenoma thyroid Pedunculated fibroid Cyst of ovary

There was narrowing of both renal orifices and both the renal arteries were small when compared with the superior mesenteric The kidneys were not particularly enlarged Both contained numerous cysts ranging in size from 3 cm down to a few millimeters There was a great deal of renal tissue remaining

The renal symptoms and uremia were the result of marked intrarenal arteriosclerosis and arteriolosclerosis superimposed on kidneys already damaged by congenital polycystic disease There was also generalized arteriosclerosis and severe arteriolosclerosis associated in many regions with small fresh and organizing thrombi These produced small focal myocardial scars and small areas of encephalomalacia There were heart failure and chronic passive congestion

SUMMARY This 61 year old white woman had puffiness of the eyes and urinary frequency for 12 months Three months before death she had failing vision and was found to have hypertension and anemia Nausea and vomiting developed and she was admitted two weeks before death in severe uremia with hypertension anemia severe vascular retinitis and a tender mass in the right upper quadrant The urine specific gravity was low albuminuria slight and only an occasional cast appeared in the sediment Analysis of the findings indicated a circumscribed type of renal disease The mass was interpreted as a polycystic kidney and it was thought that vascular disease had contributed to the final development of renal failure and uremia CONGENITAL POLYCYSTIC KIDNEYS were found at autopsy and there was also an arteriosclerotic and arteriolosclerotic nephritis



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Chapter 6

HEMATEMESIS AND MELENA

ONE OF THE MOST difficult problems in medicine is the diagnosis and management of cases of severe gastrointestinal hemorrhage The patient is usually very ill and the nature of the condition limits the scope of the examination Judgment must be based on the full consideration of every available fact

Although it is generally true that the occurrence of melena without hematemesis indicates a lesion distal to the pylorus this is not an invariable rule Melena without hematemesis may be seen following rupture of an esophageal varix or in gastric carcinoma On the other hand if the patient vomits large amounts of blood one can feel *reasonably* certain that the lesion *is in either the esophagus stomach* or duodenum Bright blood in the stools is usually but not invariably indicative of hemorrhage low in the intestine with hypermotility and active bleeding it may be observed in patients with lesions in the esophagus stomach or duodenum The gross appearance of vomited blood has no important diagnostic significance Coffee ground vomitus may be seen in peptic ulcer and bright blood vomitus in patients with gastric carcinoma although the old teaching has been that the reverse is invariably the case The amount of blood vomited *before the patient comes under* observation may be difficult to estimate the patient s imagination and fright may affect his estimate and admixture of gastric contents is an important variable Azotemia and pyrexia may be associated with the presence of old blood in the gastrointestinal tract

Severe melena of obscure origin has been discussed by Stone in an analysis of 79 cases seen by him He focuses on the diagnostic problem presented by the patient who having no knowledge of any previous gastrointestinal disturbance suddenly passes a large amount of bright red to tarry blood per rectum The lesions causing this type

of hemorrhage are numerous and include peptic ulcer carcinoma of the stomach cyst or diverticulum of the duodenum esophageal varices acute gastroenteritis regional ileitis Meckel s diverticulum carcinoma of the colon ruptured vessel in the rectal wall lymphoid or myeloid leukemia hemophilia familial telangiectasia polyps other intestinal tumors aneurysms etc In 34 cases no definite cause for the bleeding was ever found In this relatively large group of cases of hemorrhage of unknown origin the negative conclusions were reached by means of clinical diagnostic studies occasionally followed by exploratory operations The results are in accord with the general experience that in many cases the location and cause of the bleeding cannot be determined Even in cases which come to autopsy following massive hemorrhage a careful search of the entire length of the gastrointestinal tract may fail to disclose the source of the hemorrhage

Table 9 Causes of Hematemesis and Melena

I *Lesions of the gastrointestinal tract*

A Ulcerative lesions without infection
1 Esophageal ulcer (cardiospasm scleroderma)
2 Peptic ulcer
3 Ulcerative colitis
4 *Fissures and fistulae*
5 Acute necrosis due to chemical agents
6 Neoplasms
a Benign polyps leiomyomas
b Carcinoma and sarcoma (esophagus to rectum)
7 Hiatus hernia
8 Intussusception

B *Infection with or without ulceration*
1 Dysentery (amebic bacillary)
2 Typhoid fever
3 Parasitic infestation
4 Actinomycosis
5 Syphilis
6 Tuberculosis
7 Gastritis and gastroenteritis

C Congenital hereditary other
1 Meckel s diverticulum
2 Esophageal gastric duodenal and colonic diverticula
3 Pseudoxanthoma elasticum
4 Intestinal lipodystrophy

II Associated with rupture of esophageal varices secondary to portal hypertension due to

- A Extrahepatic lesions
  - 1 Thrombosis of hepatic veins (Chiari s syndrome)
  - 2 Thrombosis of portal vein
    - a Infection
    - b Compression
    - c Tumor invasion
    - d Blood dyscrasia
  - 3 Stricture or cavernous transformation of portal vein
  - 4 Congenital anomalies
- B Hepatic causes
  - 1 Cirrhosis (portal biliary post necrotic Banti s syndrome)
  - 2 Hemochromatosis
  - 3 Syphilis
  - 4 Sarcoidosis
  - 5 Schistosomiasis
  - 6 Hepatolenticular degeneration

III Vascular Lesions

- A Hypertension
- B Embolism and thrombosis of mesenteric vessels
- C Polyarteritis due to
  - 1 Periarteritis nodosa
  - 2 Systemic lupus erythematosus
- D Leakage of aneurysm (syphilitic arteriosclerotic mycotic dissecting)
- F Hereditary telangiectasia

IV Blood dyscrasias and deficiency diseases

- A Purpura (thrombocytopenic non thrombocytopenic)
- B Hemophilia
- C Leukemia
- D Hypoprothrombinemia
- E Scurvy
- F Aplastic anemia
- G Other diseases associated with defects in the coagulation mechanism

Figures as to the frequency of the various causes of massive gastrointestinal hemorrhage vary from clinic to clinic but in general peptic ulcer contributes about 50 per cent of the cases hepatic cirrhosis about 10 per cent gastric carcinoma 3 per cent gastritis 1–2 per cent miscellaneous causes 7–8 per cent and undetermined causes 25 per cent The commonest causes of hemorrhage from the gastrointestinal tract are listed in Table 9

Let us examine in more detail the points of importance in differentiating the three diseases most commonly responsible for massive hemorrhage The patient may be seen for the first time while acutely ill from blood loss and a history may be difficult to obtain Single large unheralded hemorrhages come frequently from peptic ulcer Intermittency of bleeding is common in this disease probably because of digestion of the thrombus by the highly acid juices A history of periodic pain particularly if relieved by food or alkali is very significant Hemorrhage from ulcer frequently occurs also in aging people and often in them a brisk hemorrhage is the only clinical symptom of the presence of the ulcer Disregarding this fact may lead to the mistaken diagnosis of carcinoma of the stomach

Bleeding in cases of gastric carcinoma is usually due to ulceration of the stomach or necrosis and sloughing of papillary growths The vessels involved are usually small and oozing rather than massive hemorrhage results However in the late stage bleeding from a larger vessel may occur within a carcinomatous ulcer In most instances when a massive hemorrhage occurs even superficial examination of the abdomen will reveal a mass leading one to suspect the presence of carcinoma Massive bleeding may occur in a benign ulcer in which carcinomatous change has developed

Recognition of hemorrhage from rupture of an esophageal varix depends on the ability to find evidence of obstruction to the portal or splenic veins Hemorrhoids or dilated abdominal veins may be present The elevation of portal venous pressure serves to enlarge the venous communications between the gastric and esophageal veins resulting in fragile varicosities which are best seen on careful barium study of the lower esophagus Ascites of course may be detectable and the liver and spleen may be palpable In most instances if this evidence is present one can safely conclude that the hemorrhage came from a ruptured varix Hematemesis may be the first manifestation of the disease in about 10 per cent of the cases of cirrhosis of the liver Peptic ulcers occur more commonly in patients with cirrhosis of the liver than in the general population Bleeding may be from such a lesion even though esophageal varices can be demonstrated

The recognition of some of the less common causes of massive gastrointestinal hemorrhage although difficult in many instances may prove to be of great practical value Gastritis may be assumed to be the cause of hematemesis only if no other pathologic changes have been found and there is confirmatory gastroscopic evidence Other less common causes include rupture of an aortic aneurysm into the

esophagus tumor eroding the duodenum esophageal lesions with ulceration hiatus hernia with erosive gastritis congenital varicosities of gastric veins carcinoma of the esophagus mesenteric thrombosis and various blood dyscrasias Hereditary telangiectasia may involve the gastrointestinal tract with recurrent massive hemorrhage

Following the passage of blood per anum the first step is to rule out local causes such as hemorrhoids and fissure by means of visual and digital examinations A variety of rectal diseases including local infections polyps and malignant lesions may be complicated by hemorrhage but these may be readily detected by proctoscopic study Tissue may be obtained for biopsy when indicated When the lesion cannot be reached by the proctoscope or sigmoidoscope x ray studies may yield crucial information

A variety of tumors of the small and large intestine may give rise to bleeding Benign tumors such as polyps and hemangiomas are more apt to cause large hemorrhages than are malignant neoplasms Diverticula of various sorts must not be overlooked Hemorrhage of massive degree may develop with erosion of the mucosa in a Meckel s diverticulum or from the hemangioma like vascular channels of a thin walled colonic diverticulum which has become infected Other causes are trauma from ingested foreign bodies and erosion from pressure of extra intestinal lesions

A variety of specific infections may result in ulceration leading to hemorrhage Tuberculous ulcers are most commonly seen in the ileum and ileocecal region Encircling ulcers leading to severe hem orrhage may be due to syphilis Actinomycosis may also be the basis of melena A systemic reaction to the infection may be absent in these cases in contrast to the situation when the hemorrhage results from amebic or bacillary dysentery Other types of colitis which may be associated with severe bleeding are the non specific ulcerative variety and that seen as a complication of uremia

Some type of blood dyscrasia should always be kept in mind since severe intestinal hemorrhage may be an early sign of thrombocyto penic purpura or acute leukemia *A variety of vascular lesions must* be considered Melena may result from embolism of the upper branch of the superior mesenteric artery This occurs most often in the course of bacterial endocarditis Thrombosis of the mesenteric veins leading to hemorrhage may result from abdominal injury or from infection with complicating phlebitis Abdominal pain and hemor rhage may be prominent features in cases of periarteritis nodosa

Illustrative Cases

I

(#471635 Admitted Aug 20 1948 Died Sept 8 1948)

This 67 year old huckster was admitted because of hematemesis and melena of two days duration

One year before admission he began to have pain just above the umbilicus which appeared about two hours after meals and was relieved by milk Occasionally he had pain at night For six months he noticed anorexia Two weeks before entry his pain became more frequent and severe appearing often at night and in the morning before breakfast It was always relieved by eating He complained of some diarrhea Two days before entry he passed several loose tarry stools and vomited some brown coffee ground material Vomiting of similar material occurred again the next day

PHYSICAL EXAMINATION on admission T 98 8 P 108 R 22 B P 65/45

The patient was in shock and quite restless The skin was pale and dry There was no lymph node enlargement The pupils reacted well and funduscopic examination showed no abnormalities The few remaining teeth were carious The heart and lungs were normal The abdomen was soft there was no tenderness and no organs or masses were detected on light palpation Neurological examination revealed no abnormalities

LABORATORY DATA *Hemoglobin was 6 5 gm leukocytes 14 500* with normal differential Urine showed no abnormalities but the stools were tarry and liquid

COURSE IN THE HOSPITAL After the transfusion of 1 000 ml of blood the blood pressure rose to 100/80 and the hemoglobin to 7 8 gm The following day the patient was again in shock and passed several bloody bowel movements Following further transfusions his condition improved On August 22 the patient had a rather severe transfusion reaction with a shaking chill and rise in temperature to 104 2 Following this he vomited an undetermined amount of bright red blood and again went into shock

Operation was performed on August 23 During the operation 2 500 ml of blood was given There was old blood in the small intestine and in the colon but very little in the stomach There was no evidence of any ulcer

in the duodenum but in the cardiac portion of the stomach a large hiatus hernia was found The stomach could easily be pulled down into the abdominal cavity A subtotal gastrectomy was done and an anterior Polya anastomosis performed Microscopic examination of the specimen showed chronic gastritis

He did well for a few days after operation On August 27 he vomited 200 ml of bright red blood and blood pressure dropped to 65/40 His condition improved after transfusion On August 31 when he was apparently doing well and had begun to take food by mouth he suddenly vomited 50 ml of bright red blood and went into profound shock with a blood pressure of 30/20 He was given 1500 ml of blood and his pressure rose slowly to 115/50 On September 1 a non manipulative gastrointestinal series was done and the congenitally short esophagus or hiatus hernia was demonstrated No esophageal varices were seen Approximately 80 per cent of the stomach had been resected There was prompt emptying by way of the efferent loop and no lesions were noted in that portion of the stomach which remained or in the anastomotic site Six hours after this procedure he vomited 200 ml of dark coffee ground material and 15 minutes later 500 ml of fresh blood containing clots He responded well to transfusion On September 2 another operation was performed A thoraco abdominal exploration was carried out with total gastrectomy and resection of the lower end of the esophagus The defect in the diaphragm was approximated He was given copious amounts of blood during the procedure The following day his hemoglobin was 16 5 gm On September 3 nonprotein nitrogen was 31 mg / and total serum bilirubin 5 8 mg /$_0$ direct 4 6 On September 4 a portable chest film showed pleural fluid on the left Five hundred ml of dark brown fluid was removed The urine was found to contain a few white blood cells but no red blood cells were seen On September 7 150 ml of sour smelling red fluid was removed from the left pleural cavity On September 8 the patient suddenly became dyspneic and the blood pressure dropped to 40/30 Whole blood was started immediately and the pressure rose to 90/60 Thoracentesis yielded only 50 ml of red fluid A few hours later he suddenly ceased breathing

Material removed from the pleura on September 6 showed no growth on culture That removed on September 7 showed beta streptococcus proteus and *A aerogenes*

Discussion There are two distinct problems in this case both of which must be answered in order to provide a satisfactory explanation of the facts The first is the site and cause of the hemorrhage and the second is the cause of the jaundice and of his death a few days after the second major operative procedure

This case seems to point out the fallacy in the old clinical aphorism that coffee ground vomitus is indicative of a gastric carcinoma and bright blood suggests benign ulceration The fact that there were repeated hematemeses is highly suggestive that the site of hemorrhage was above the jejunum To be sure he did pass bright blood in the

stools on occasion which would suggest bleeding at a lower level However with blood in the intestinal tract hypermotility may result and the evidence is still in favor of a lesion higher up unless there were multiple bleeding points

Peptic ulceration or carcinoma of the stomach or duodenum would seem to be ruled out as the entire stomach was removed and examined and the duodenum was opened at operation and explored It is unlikely that a carcinoma was overlooked but in spite of the direct visualization and the normal duodenal x ray the possibility of a bleeding duodenal ulcer must be kept in mind as it is the commonest cause of massive intestinal hemorrhage and often difficult to detect even at laparotomy The history is quite compatible with such a diagnosis It might be difficult to explain the diarrhea unless the lesion was adjacent to the pancreas with invasion of that structure

There was nothing in the history or physical examination to suggest hepatic cirrhosis No varices were seen in the x ray studies and no mention of the liver was made by the operating surgeon Varices are usually quite low in the esophagus and should have been noted when the structure was seen at the second operation

A hiatus hernia was seen at both operations Since there is no proof that there was further bleeding after the second operation one might suppose that the bleeding point had been removed It is difficult to evaluate the finding of a *diaphragmatic hernia* Some patients with this condition show a severe anemia due to chronic blood loss but a sudden exsanguinating hemorrhage is rare The cause of the bleeding in these cases may be difficult to determine but such bleeding is often due to mucosal erosions in the region of the constricting ring of the hernia Division of the phrenic nerve and manipulation of the hernial orifice at the time of operation may have relieved the tension on the gastric mucosa It is difficult to attribute this man s symptoms to hiatus hernia These lesions may produce no symptoms or they may mimic closely such widely divergent diseases as peptic ulcer angina pectoris or chronic cholecystitis or give manifestations suggesting esophageal obstruction The symptoms may be made worse by the horizontal position One might interpret his pain on awakening on such a basis The symptoms are usually not relieved by an ulcer regimen One may suspect hiatus hernia when symptoms have been present without progression over a number of years, when there are epigastric or para umbilical cramps usually one half to one hour after meals relieved by induced vomiting but not by food when symptoms resembling chronic cholecystitis are provoked by

assumption of the horizontal posture after meals when there are postprandial angina like symptoms without evidence of cardiac disease, when there is a long history of slight dysphagia and when there is an unexplained anemia Once the condition has been suspected it is best demonstrated by x ray studies of the patient in the horizontal position The presence of a hernia was not suspected in this case before the x ray examination No other lesion was found at operation It may be significant that bleeding continued after the first operation while the hernia was still demonstrable by x ray However in view of the fact that massive sudden bleeding is rare that his symptoms were relieved by food and that there was a large hiatus through which the hernia could be easily reduced hernia as the cause of the bleeding is unlikely

In the early stages of the illness the symptoms were compatible with an uncomplicated duodenal ulcer Then the pain became more severe awakening him at night and for two weeks he had mild diarrhea This suggests the possibility that the ulcer had penetrated to the pancreas with some resulting pancreatitis The bleeding area was probably above the jejunum and the course of the illness was compatible with a posterior ulcer of the duodenum with penetration of the pancreas

The only other feasible diagnosis is *syphilitic aneurysm* with erosion into the esophagus This should have led to a more rapid exsanguination There was no evidence of aortic dilatation in this region and such a diagnosis does not fit the story of epigastric pain relieved by food The diarrhea may have been due to a lesion lower in the bowel—ulceration polyps or diverticula such lesions would not be accompanied by hematemesis if bleeding took place

The long illness with persistent shock the infection of the pleural fluid which accumulated after the second operation the multiple transfusions often accompanied by a febrile reaction the absorption from the bowel of the degradation products of old blood may all have contributed to the development of jaundice There may have been a spreading reaction with edema about the ulcer site which led to partial biliary tract obstruction One cannot be certain as to the cause of the icterus The sudden dyspnea and shock relieved temporarily by transfusion and followed a few hours later by death suggests a final fatal hemorrhage from the site of previous bleeding in the duodenum

ANATOMICAL DIAGNOSIS (Autopsy No 21389) Chronic duodenal ulcer Perforation and thrombosis of gastroduodenal artery History of

subtotal gastrectomy and repair of hiatus hernia Subsequent total gastrectomy with resection of lower end of esophagus esophagojejunostomy and jejunojejunostomy Localized fibrinous peritonitis Ascites Encapsulated empyema at base of left lung posteriorly Abscess of left thoracic and abdominal wall communicating with left empyema cavity and operative wound Tubular degeneration of adrenals History of multiple transfusions Hemosiderin in spleen Few hemoglobin casts in kidneys Jaundice Pulmonary edema Bilateral cortical adenomas of adrenals Massive necrosis of left adrenal cortical adenoma Chromophobe adenoma of pituitary

The duodenal ulcer was chronic and healing but it had perforated the gastroduodenal artery in its base The vessel was now thrombosed The second surgical intervention had resulted in a localized empyema at the site of anastomosis of the jejunum and esophagus The jejunojejunostomy was healthy The empyema communicated with a large abscess that covered the left thoracic and upper abdominal wall and communicated in turn with the abdominal incision The central liver cells were moderately atrophied but there was no central necrosis The jaundice must have been due to a combination of *infection anoxemia and perhaps hemolysis*

SUMMARY This 67 year old man for one year had had postprandial pain relieved by food He developed persistent hematemesis which led to operation at which a hiatus hernia was found After partial gastrectomy he continued to bleed and at a second operation total gastrectomy was performed He developed empyema became jaundiced and suddenly died Autopsy revealed a CHRONIC DUODENAL ULCER In review the characteristic symptoms and the frequency of large hemorrhage from duodenal ulcer might have led to the diagnosis even with the negative x ray and operative findings The course of the illness was not typical of hiatus hernia and acute massive hemorrhage from such a hernia is unusual

II

(#468831 Admitted July 30 1948 Died July 31 1948)

THIS 64-year old accountant fainted two hours before admission His dietary intake had been adequate and he was not a user of alcohol

Six years before death he developed intermittent pain in the upper portion of the abdomen accompanied by flatulence heartburn and sour eructation which were partially relieved by powders These symptoms increased in severity six months before examination The pains became more frequent and severe continuing throughout the night He took powders occasionally with some relief but for several months had disliked eating because of the discomfort which followed He had lost 25 pounds in the previous six months On July 23 physical examination revealed a normal pulse rate and blood pressure with no fever He was undernourished He had geographic tongue but there was no papillary atrophy The heart was normal blood pressure was 120/80 There was thickening of the peripheral arteries The abdomen was prominent in the upper portion The veins were conspicuous particularly over the upper abdomen The right upper abdomen was filled by a hard slightly nodular mass which extended across the epigastrium and was tender the edge being felt 6 cm below the costal margin in the midclavicular line The spleen was not enlarged The cecum was palpable and felt boggy The reflexes were normal

The blood serologic test for syphilis was negative The stool contained no ova or parasites and the guaiac test was negative The urine was normal Examination of the blood showed red count 5 06 million hemoglobin 12 gm hematocrit 42% sedimentation rate 31 mm per hour leukocyte count 6 550 with a normal differential Examination of the gastric contents revealed free hydrochloride acid 18 total acid 38 Bromsulfalein test of liver function showed 33% retention in half an hour On x ray examination the colon contained a large amount of gas and fecal material but there was no evidence of any organic lesion The terminal ileum did not fill Gastrointestinal series on July 27 showed esophagus stomach and duodenum normal Repeat examination on July 30 showed the presence of barium from the previous examination After introduction of the barium the greater curvature close to the pylorus was found to be soft pliable freely movable and without any real evidence of organic disease but on the films this region appeared slightly irregular It was the impression however that no organic lesion was present

On July 30 1948 the patient became short of breath After his examination while shopping he developed pain in the precordium and upper abdomen and fainted

At that time temperature was 98 pulse 98 respirations 20 blood pressure 88/60 The patient was extremely pale but otherwise there was no significant change from the previous examination

Hemoglobin on admission was 9 5 gm urine normal blood nonprotein nitrogen 53 mg % prothrombin time 45% of normal Electrocardiogram showed borderline low amplitude of the QRS complexes but no changes suggestive of coronary occlusion

Forty five minutes after eating he suddenly vomited 250 ml of dark blood following which there was a further drop in blood pressure After a 500 ml transfusion his pressure returned to normal but three hours later he vomited 200 ml of dark blood with clots once more going into shock During the next 12 hours he continued to vomit blood and was in shock despite the administration of three liters of whole blood An exploratory laparotomy was done and he died postoperatively in shock

DISCUSSION In this case there was a relatively complete diagnostic study shortly before the hemorrhage The two x rays of the gastrointestinal tract failed to demonstrate a clear cut lesion On physical examination a large and firm liver was palpated The laboratory and special examinations provided no critical diagnostic information so that one must rely mainly on the clinical facts to determine the type of disease present

In view of the massive hematemeses it seems certain that the bleeding point was above the jejunum It is not possible to exclude an esophageal lesion on the ground that he bled sufficiently to go into shock before vomiting blood Blood from the esophagus may trickle into the stomach be changed in color by contact with the gastric juice and be sufficient in amount to produce shock before any material is vomited

In view of the history the course of the bleeding and the finding of a large firm liver, the following diagnoses must be considered cirrhosis of the liver possibly with primary carcinoma of the liver duodenal ulcer or carcinoma and gastric ulcer or carcinoma

In considering the diagnosis of cirrhosis of the liver it would be helpful to determine whether the hepatomegaly was due to fatty infiltration or whether the patient had portal obstruction and fatal hemorrhage from an esophageal varix Impairment of liver function was indicated by the bromsulfalein test and possibly the reduced prothrombin activity There was on the other hand no objective evidence of portal hypertension such as splenomegaly or ascites The prominent abdominal veins might have been due to the recent loss of weight and in themselves be of no great significance Patients with a degree of cirrhosis sufficient to result in esophageal varices which bleed profusely usually do not have such conspicuous hepatomegaly

unless a complicating primary liver tumor has developed In any event primary liver disease would probably not account for the degree of epigastric pain and discomfort of the type which the patient experienced Duodenal ulceration is not infrequently seen in patients with cirrhosis of the liver and such a lesion in a patient recently seen was the source of a severe hemorrhage Early in the illness in the present case the pain was partially relieved by powders However six months before death the pain grew worse was more constant and was aggravated by food There was no vomiting to suggest obstruction and altogether the story is not typical of duodenal ulcer There was no x ray evidence of a lesion of the esophagus or duodenum This helps to exclude carcinoma of the duodenum which is rare in any event

The vagueness of the history and the changing effect of food intake might be more compatible with a gastric ulceration than with a peptic ulcer of the duodenum particularly if the lesion were high in the stomach Benign gastric ulcers not infrequently bleed profusely with persistent hematemesis

However one cannot neglect the implications of the large and hard liver in an elderly male The absence of splenomegaly seems to rule out various diseases of the blood forming organs and lymphatic system as a cause of the hepatomegaly It also leads one to lay aside a diagnosis of cirrhosis and primary carcinoma of the liver and think of metastatic neoplasm of the liver because this is a common cause of marked hepatomegaly when there is no enlargement of the spleen

This conclusion having been reached the next question concerns the site of the primary neoplasm The vague but definite story of epigastric discomfort aggravated by food suggests gastric carcinoma a relatively common disease in a white male of this age However in reviewing the detailed findings certain discrepancies appear Massive hemorrhage from carcinoma of the stomach is unusual but may occur Although patients with carcinoma of the stomach usually have no free hydrochloric acid again this is not an infallible rule However the lesion must be in the upper gastrointestinal tract and the only localizing feature besides the history and the hepatomegaly is the suggestion of an irregularity along the greater curvature of the stomach on x ray examination

This with the other clinical facts points to carcinoma of the stomach with metastases to the liver as the most likely diagnosis

Anatomical Diagnosis (Autopsy No 21323) Chronic peptic ulcer above pylorus with fresh erosion and hemorrhage Infected thrombus

(gram positive rods and cocci) adherent to base Gastric hemorrhage Adenocarcinoma arising from margin of ulcer with invasion of its base Metastases to regional lymph nodes and liver Thrombosis splenic vein Recent laparotomy Aspiration with lobular pneumonia Pulmonary edema

At a point very close to the pylorus along the lesser curvature there was a large shallow ulceration about 3 cm in diameter and 1 mm in depth The edges were not raised and did not feel hard Lymph nodes along the lesser curvature showed tumor metastases Throughout the liver there were tumor nodules of varying size The splenic artery shortly before its junction with the superior mesenteric was distended with thrombus material which protruded into the portal vein

Microscopically there was a chronic gastric ulcer with fibrous thickening of the distorted stomach wall and a generous layer of granulation tissue forming its base There was recent necrosis which had eroded a vessel in the granulation tissue with resulting hemorrhage In section a thrombus was still adherent to the base of the ulcer In the deepest portion of scarring forming the wall of the ulcer adenocarcinoma was invading lymphatics but the ulcer itself did not appear to be the result of necrosis in an established carcinoma In one section taken from the margin of the ulcer the carcinoma seemed to arise from or at least be continuous with adjacent normal mucosa The gastric hemorrhage arose from the ulcer rather than from the carcinoma

SUMMARY This 64 year old white man had a six year story of intermittent pain and of heartburn partially relieved by powders Six months before death pain became more severe and was aggravated by food Examination revealed loss of weight and hepatomegaly There was free acid in the gastric juice and bromsulfalein retention was 33% Gastrointestinal series showed suggestive irregularity along the greater curvature He suddenly vomited dark blood remained in shock despite transfusions and died postoperatively The story of pain aggravated by eating the hepatomegaly and the radiological findings led to a diagnosis of gastric carcinoma in spite of the presence of free hydrochloric acid and the fact that massive hemorrhage occurs infrequently from a carcinomatous ulcer The early history and the subsequent developments were adequately explained by the finding of both an ULCER AND A CARCINOMA OF THE STOMACH the hemorrhage having resulted from erosion of a vessel in the base of the ulcer

III

(#404072 Admitted Nov 6 1946 Died Nov 17 1946)

THIS 54 year old Negro woman was admitted because of severe rectal bleeding In 1936 she was seen because of a positive Wassermann Examination showed extreme obesity The heart was not enlarged There were numerous varices and she complained of pain and swelling of the legs Antisyphilitic treatment was begun but was continued for only a short period

Three years before admission she had an episode of rectal bleeding which was readily controlled She passed several bloody stools with numerous clots Five days before admission she again began to pass clots of blood The night before entry the bleeding was profuse and she became very weak There was no nausea or vomiting and no pain There had been no weight loss change in bowel habits digestive symptoms or diarrhea Several years previously she had complained of vague epigastric distress unrelated to meals but relieved by Sal Hepatica After a transfusion she improved

PHYSICAL EXAMINATION on admission T 100 P 108 B P 160/70

The patient was obese The pupils reacted sluggishly to light and accommodation Funduscopic examination was normal The mucous membranes were pale There was no lymph node enlargement The lungs were clear The heart could not be outlined accurately on percussion There was an apical systolic murmur There was an exceedingly thick abdominal panniculus No tenderness or masses were made out None of the viscera were felt There was no edema On rectal examination no mass or stricture was felt Pelvic examination was normal

LABORATORY DATA Hemoglobin 4 gm red blood cells 1 4 million leukocytes 14 400 with 1/ myelocytes 11% juvenile neutrophils 66/ segmented neutrophils 11/ lymphocytes and 11% monocytes Bleeding time was 3½ min clotting time (capillary method) 4 min platelet count 133 000/cu mm Icterus index 5 sedimentation rate 11 mm per hour (uncorrected) nonprotein nitrogen 60 mg % chloride 99 4 mEq /L Urine was normal Serologic test for syphilis negative Stool grossly positive for blood no ova or parasites seen Gastric analysis showed no free hydrochloric acid or blood

COURSE IN THE HOSPITAL A vein was cannulated in order to administer blood Later due to thrombophlebitis a second vein had to be cannulated Two days after admission the platelet count was 62 000 During the first few days there were several episodes of rectal bleeding

When a proctoscopic examination finally could be made no bleeding point was found With transfusions the hemoglobin rose to 12 5 gm Three days after admission the patient developed cough and wheezes in both lung fields Five days later the temperature began to rise as did the leukocyte count On the day before death she was started on sulfamerazine as there was no response of the temperature to penicillin More rhonchi developed in the lungs her condition grew steadily worse and she died

DISCUSSION This case presents two problems (1) the cause of the rectal bleeding and (2) the cause of death

With regard to the first question we want to know whether there was any abnormality of the blood Rectal bleeding may occur in certain of the blood dyscrasias and acute leukemia or thrombocytopenic purpura must be considered

It would seem unlikely that this patient had an acute leukemia as there were no abnormal white cells in the circulating blood other than such young forms as one would expect after severe hemorrhage The constitutional features of an acute leukemia were not present

The possibility of thrombocytopenic purpura is suggested by the platelet count of 62 000 and also by the fact that there was a great deal of fresh bleeding from the rectum In addition to fresh blood clots were passed from time to time and the bleeding time and clot retraction were normal In the presence of a severe hemorrhagic anemia one would expect the platelet count to rise on the other hand with such extensive rectal bleeding from purpura one would expect bleeding elsewhere particularly from other mucous membranes the mouth or vagina

It would seem then that the bleeding came from some lesion in the gastrointestinal tract No blood was found in the stomach nor was there any vomiting of blood With an ulcer of the duodenum one may bleed profusely by rectum and there was a history of epigastric distress for several years The high nonprotein nitrogen the day after admission suggests the possibility of prerenal azotemia but there was no evidence that old blood was retained in the intestinal tract The dehydration and low arterial pressure seem sufficient to account for the high nonprotein nitrogen

If the blood came from low down in the gastrointestinal tract as seems more likely it is important that mucus and pus were not described in the stools Furthermore there were no local symptoms such as abdominal pain tenesmus, diarrhea or alteration of the bowel habits On proctoscopic examination no lesion was found Although such profuse bleeding might occur with carcinoma of the

rectum or sigmoid it would be unusual and it is reasonable to assume that the bleeding of three years before had occurred from the same source With such profuse bleeding and without symptoms a benign lesion such as a polyp diverticulosis or a hemangioma is the most likely source

The patient continued to bleed, although she recovered from the shock present on admission After several days she developed rather diffuse signs in the lungs with a rise in temperature and elevation of the leukocyte count Infection was suspected and she was treated with penicillin and sulfamerazine with no response A vein had been cannulated for transfusion This became thrombosed It would seem likely that the signs in the lungs were due to pulmonary emboli

ANATOMICAL DIAGNOSIS (Autopsy No 20269) History of massive bleeding per rectum Multiple diverticula of colon History of numerous transfusions by means of cut downs of veins of both ankles Thrombo *phlebitis of superficial vessels of both ankles Multiple septic emboli to* lung with mycotic aneurysm formation infarction and beginning abscess formation Acute splenic tumor Hyperplasia of bone marrow Slight dilatation and hypertrophy of heart Central atrophy of liver

There were multiple diverticula in the colon The large bowel was full of blood but the actual bleeding point was not demonstrated Microscopic sections of these diverticula showed thinning and absence of the muscle in such areas leaving only the epithelium and connective tissue Noted in the connective tissue was the regular occurrence of large blood channels presumably veins and the bleeding was probably from such a source These dilated blood channels really constituted a hemangiomatous area An underlying infection of the diverticula might have caused the erosion of a vessel No polyp was present The lungs showed multiple emboli which were infected and there was a staphylococcus albus in the heart s blood From the infected emboli multiple small abscesses in the lungs had developed

SUMMARY This 54 year old Negro woman entered because of severe bleeding from the rectum She had a similar episode three years previously She was obese and in shock so a leg vein was cannulated to facilitate trans fusion It became thrombosed Fever leukocytosis and diffuse pulmonary signs developed There was no response to antibiotics Proctoscopic exami nation revealed no source of bleeding In view of the profuse melena with out local symptoms the previous episode of hemorrhage and the negative proctoscopic examination it was thought that the lesion was benign and either a polyp diverticulum or hemangioma At autopsy multiple DIVERTICULA OF THE COLON were found There were septic emboli in the lungs

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Chapter 7

JAUNDICE

JAUNDICE IS ONE of the manifestations of a wide variety of diseases In many cases it is such a conspicuous and alarming development that it serves as the primary reason for seeking medical advice In other instances it is so slight that it is overlooked by the patient and it may even escape the attention of the unwary physician Slight degrees of jaundice are best detected in the scleras under day light *illumination Considerable degrees of jaundice may escape de* tection under artificial illumination The term *subclinical jaundice* is applied to those cases in which the blood bilirubin is not elevated to a degree or for a length of time sufficient to cause visible staining of the tissues Even when the jaundice is subclinical its detection may be an important key to the correct diagnosis

Substances other than bile pigments may cause coloring of the skin which is mistaken for jaundice Some of these substances e g caro tene may also give a yellowish tinge to the serum and thus give a falsely high icteric index Carotenemia does not cause discoloration of the scleras During World War II when antimalarials were being widely used the yellow coloring of the skin produced by Atabrine was a familiar sight in military personnel This type of pigmentation is most conspicuous in people of dark complexion It is less readily detected in the scleras than in the skin It may persist for several weeks after use of the drug is discontinued Picrates may also give a yellowish color to the skin The bronze color of hemochromatosis may sometimes be confused with the dull greenish brown jaundice seen in cases of long standing biliary tract obstruction However the pigmentation of hemochromatosis does not involve the scleras Al though pigments other than bilirubin may give a high icteric index they do not give the van den Bergh reaction In some cases e g in carotenemia the pigment may be identified by chemical tests

Table 10 Causes of Jaundice

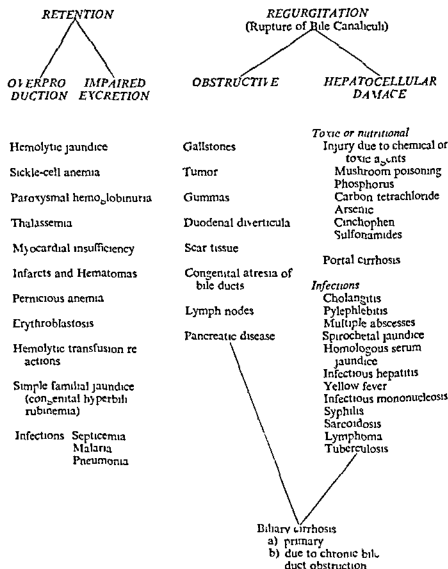


Table 10 presents the causes of jaundice listed in accordance with a classification first proposed by Rich For purposes of differential diagnosis all causes of jaundice may be placed in either the *retention* or the *regurgitation* group There are cases in which both retention and regurgitation play a part in the production of jaundice There are also cases in which the laboratory data do not permit one to make a sharp differentiation between the two Nevertheless the classi

fication is a very useful one and in most instances if it is kept in mind careful integration of the clinical and laboratory data will lead to a correct diagnosis

As indicated in the table jaundice occurs under two sets of circum stances (1) when there is an overproduction of bilirubin and a diminished capacity of the liver to excrete this pigment (retention jaundice) (2) when there is an interruption in the continuity of the cells lining the bile passages allowing the secreted bile to flow back into the blood stream (regurgitation jaundice) In the differential diagnosis of jaundice the first step is to determine whether the case falls into the first or the second of these broad categories

Retention jaundice is characteristically encountered in diseases in which there is some abnormality of the red blood corpuscles such as hemolytic jaundice of the congenital or acquired type sickle cell anemia or pernicious anemia Excessive destruction of morphologi cally normal corpuscles such as occurs in hemolytic transfusion reac tions paroxysmal hemoglobinuria and erythroblastosis leads to the same type of jaundice In most cases of retention jaundice there is in addition to excessive liberation of hemoglobin evidence of anoxic damage to the liver cells The anoxia may be due to the associated anemia or to poor aeration of the blood as in cases of congestive heart failure or pneumonia Damage to the liver alone is usually not the cause of retention jaundice unless it is associated with increased liberation of hemoglobin For example one may have extreme chronic passive congestion of the liver without jaundice The sudden development of retention jaundice in such a case frequently is indic ative of the occurrence of pulmonary infarction with resulting de struction of red blood corpuscles

In cases of retention jaundice the history physical examination and hematological examination may point clearly to the correct diag nosis without more elaborate tests However it is well to remember that in some of the chronic hemolytic diseases such as congenital hemolytic jaundice and sickle cell anemia gallstones are prone to develop and that these may cause a complicating obstructive type of jaundice The features of retention jaundice which help to distinguish it from the regurgitation variety are (1) usually a less intense jaun dice less even than one would expect from the level of the blood bilirubin and of a color which is more in the orange than in the green range of yellow (2) the presence of bile in the feces (3) the absence of bile and presence of urobilinogen in the urine (4) the

Table 10 Causes of Jaundice

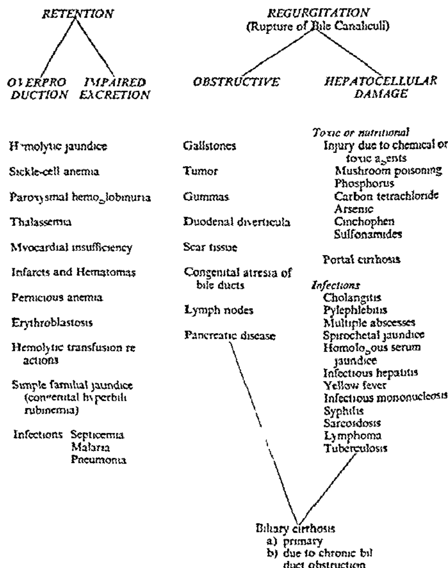


Table 10 presents the causes of jaundice listed in accordance with a classification first proposed by Rich For purposes of differential diagnosis all causes of jaundice may be placed in either the *retention* or the *regurgitation* group There are cases in which both retention and regurgitation play a part in the production of jaundice There are also cases in which the laboratory data do not permit one to make a sharp differentiation between the two Nevertheless the classi

and the thymol turbidity test provide evidence of such changes by simpler methods When the hepatocellular damage is of long standing a fall in the plasma albumin level may be detected by the usual salting out methods of fractionation Although the flocculation and turbidity tests are the most sensitive indices of liver damage as opposed to biliary obstruction they have their limitations Not all types of hepatic injury provoke changes in plasma proteins detectable by these tests Moreover certain diseases of the spleen and reticuloendothelial system give rise to abnormal plasma proteins which affect the tests in a manner indistinguishable from that observed in cirrhosis or infectious hepatitis The level of serum alkaline phosphatase which is excreted by the liver and not by the kidneys rises in obstructive jaundice Although a valuable test it is not a uniformly trustworthy index of biliary obstruction It is not always perceptibly elevated in the early phases of obstructive jaundice it may be elevated in some cases of hepatocellular jaundice and it may be considerably elevated in the absence of biliary obstruction if its production has been accelerated by diseases of the bone hyperparathyroidism Paget s disease or tumor metastases The serum prothrombin level may be reduced in both obstructive and hepatocellular jaundice If the reduction is due to obstruction rather than to cellular injury parenteral injection of a water soluble preparation of vitamin K will cause the prothrombin level to rise

Of the various tests mentioned above the *flocculation* and *turbidity tests* which are as a rule negative or only slightly positive in obstructive jaundice and strongly positive in hepatocellular jaundice and the *serum alkaline phosphatase level* which is usually normal or only moderately elevated in hepatocellular jaundice and markedly elevated in obstructive jaundice provide a particularly valuable combination of diagnostic tools In some cases the results of these tests are not clear cut The addition of some of the other tests of liver function may under these circumstances give aid in interpretation At best the functional tests can be evaluated only in the light of the clinical evidence For example if the case history is typical of cholelithiasis and x ray pictures disclose a stone probably located in the common duct the therapeutic indications should not be disregarded merely because the various tests are more consistent with hepatocellular jaundice than with obstructive jaundice

The clinical picture of obstructive jaundice is as varied as its causes Severe pain such a common accompaniment of obstruction by a stone in the common duct is rarely noted when the obstruction

is due to neoplasm (It may be well to recall at this point that pain is absent in about 15 per cent of cases with obstruction due to calculi) Occasionally in cases of non obstructive jaundice a stone in the cystic duct gives rise to pain which confuses the issue Fever is more common with obstructive than with non obstructive jaundice but it may be a striking manifestation of the hepatocellular jaundice caused by leptospira and other infectious agents Charcot s intermittent hepatic fever when present is usually associated with obstruction of the common duct by calculi However this type of fever may occur when the obstruction is due to other causes such as diverticulum of the duodenum or carcinoma of the ampulla of Vater If the fever is accompanied by chills one must think not only of a suppurative cholangitis or liver abscess but also of pylephlebitis usually originating in an acute appendicitis Palpable enlargement of the liver may be observed at some stage in almost any type of jaundice If the liver is greatly enlarged hard and nodular the cause of the jaundice is usually a neoplasm Palpable enlargement of the gallbladder points strongly to an obstructive jaundice It may occasionally be moderately enlarged and tender in association with a common duct stone A large smooth non tender gallbladder is most frequently encountered when biliary obstruction has developed slowly as the result of neoplastic encroachment upon the common duct (Courvoisier s law) Such neoplasms usually arise in the head of the pancreas, the ampulla of Vater or the bile ducts In malignant disease originating elsewhere the liver may contain hundreds of metastatic nodules without there being jaundice so long as the portal lymph nodes escape Enlargement of the spleen common in jaundice of hepatocellular origin is rare in obstructive jaundice unless the spleen is the site of metastases or the portal or splenic vein is obstructed by thrombus or neoplasm In hepatocellular jaundice the splenomegaly is often accompanied by ascites and spider angiomas

Pruritus and bradycardia have long been recognized as common accompaniments of obstructive jaundice They are attributed to an elevation in the level of the bile salts in the blood Since these salts are synthesized in the liver their level is not increased when parenchymal damage depresses the capacity for synthesis

In differentiating the various types of obstructive jaundice x ray studies may be very helpful A flat film of the abdomen may disclose calcium-containing gallstones A stone may occasionally be accurately localized in the common duct Barium studies of the duodenum may also give valuable information They may reveal a diverticulum

of the duodenum a deformity in the duodenal lumen suggesting a tumor of the ampulla or a widening of the duodenal loop indicating enlargement of the head of the pancreas It should be noted that enlargement of the head of the pancreas may be due to chronic inflammation as well as to neoplasm The inflammation may cause complete biliary obstruction and give rise to progressive jaundice closely simulating that produced by carcinoma of the head of the pancreas

The time honored procedure of searching all feces for calculi when cholelithiasis is suspected may still pay handsome dividends

Hepatic cirrhosis as a cause of jaundice requires special comment In the common type of portal cirrhosis the blood bilirubin may fluctuate The elevations are usually slight and clinical jaundice is only occasionally noted In some cases of portal cirrhosis there are periodic exacerbations in the illness during which for an interval of several weeks the patient has marked constitutional symptoms intense jaundice abdominal pain fever leukocytosis and occasionally erythematous eruptions During these acute episodes patients may be subjected to operation because biliary obstruction is suspected The jaundice may completely disappear as the episode subsides When a patient dies in one of these episodes the autopsy may reveal extensive fresh necroses in a chronically cirrhotic liver (galloping cirrhosis) The sudden development of jaundice in the course of chronic portal cirrhosis is not always due to a superimposed necrotizing process Severe hemorrhage or an intercurrent infection such as pneumonia may lead to the development of intense jaundice in the absence of any fresh lesions in the liver In hepatic cirrhosis functional tests of the liver usually show evidence of hepatocellular damage without evidence of obstruction but the exceptions are too numerous to permit complete reliance on such tests For example the alkaline phosphatase particularly during the acute episodes mentioned above may be considerably elevated

Biliary cirrhosis may be secondary to a chronic obstructive lesion such as atresia or stricture of the bile ducts or common duct stone There is also a primary type of biliary cirrhosis in which the anatomical lesions lie entirely within the substance of the liver Biliary cirrhosis is characterized by long standing pruritus jaundice and massive enlargement of the liver In contrast to what one finds in portal cirrhosis there is no anemia and the nutritional status of the patient remains good throughout most of the illness Portal hypertension if present is always a late development A particular feature of biliary cirrhosis is the high level of the blood lipids After months or years

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Pruritus and bradycardia have long been recognized as common accompaniments of obstructive jaundice They are attributed to an elevation in the level of the bile salts in the blood Since these salts are synthesized in the liver their level is not increased when parenchymal damage depresses the capacity for synthesis

In differentiating the various types of obstructive jaundice x ray studies may be very helpful A flat film of the abdomen may disclose calcium-containing gallstones A stone may occasionally be accurately localized in the common duct Barium studies of the duodenum may also give valuable information They may reveal a diverticulum

Illustrative Cases

I

(#450811 Admitted February 9 1948 Died February 10 1948)

THIS 41 year old white female when first seen was in coma and deeply jaundiced She had an illness at age 28 with jaundice She was a chronic alcoholic

She had not felt well and had been losing weight for six months She had complained of headaches and noted some edema of the ankles after standing all day Four months before admission she began to have epistaxes and the headaches became more frequent For three months before admission the stools had been intermittently acholic and black in color Three weeks before entry diarrhea developed and she complained of vague epigastric pain which was apparently severe There was anorexia The night before admission she became disoriented

PHYSICAL EXAMINATION on admission T 96 2 P 84 R 24 BP 110/55

The patient was obese deeply jaundiced and in coma The skin was loose There were numerous ecchymoses and a maculopapular eruption over the trunk and extremities A few lesions were present on the palms soles and face Many spider angiomas were seen The palms were reddened She was bleeding from the gums and nasopharynx and numerous petechiae were found in the gums Nodes were palpable in the axillas There was edema over the tibias Tongue showed normal papillae Left pupil was larger than the right but both reacted to light Fundi were normal The breasts were normal There were coarse rales over the entire chest and expiration was prolonged and wheezing The heart was enlarged to the left No significant murmurs were heard There was no ascites The liver was moderately enlarged but no definite edge could be felt The spleen was not palpated Pelvic and rectal examinations were normal She moved all the extremities Tendon reflexes were slightly more active on the right than on the left in the arms Knee and ankle jerks were absent The abdominal reflexes were not obtained There was no spasticity

COURSE IN THE HOSPITAL The temperature rose to 101 4 and the patient never regained consciousness She died within 24 hours

LABORATORY DATA Red blood count 3 6 million hemoglobin 13 gm hematocrit 40 mean corpuscular volume 111 mean corpuscular

hemoglobin 36 mean corpuscular hemoglobin concentration 34 5 icterus index over 100 sedimentation rate 28 mm per hour leukocyte count 13 800 with 92% polymorphonuclear cells smear normal Prothrombin time before vitamin K 50 seconds There was no decrease in prothrombin time after parenteral administration of vitamin K Clotting time 3 minutes bleeding time 90 seconds clot retraction normal Wassermann reaction was negative Blood nonprotein nitrogen 52 mg % sugar 88 mg / CO combining power 21 6 mEq phosphorus 5 mg % alkaline phosphatase activity 8 6 units bilirubin total 43 8 mg % direct reaction 24 4 total serum protein 4 3 gm % with albumin 2 1 gm % cephalin flocculation 3 plus thymol turbidity 19 units serum amylase 85 mg / reducing substance chlorides 76 5 mEq cholesterol 120 mg % Spinal fluid on examination showed no abnormalities but was yellowish in color

Stools were black in color and grossly bloody Urine was dark brown specific gravity 1 010 albumin 3 plus occasional red blood cells and numerous casts foam test for bile was positive urobilin and urobilinogen tests were negative

DISCUSSION The severe jaundice seems the logical focus about which to center the diagnostic discussion In view of the high level of directly reacting bilirubin it was probably a regurgitation type of jaundice The relatively short duration of the illness the lack of any significant elevation of alkaline phosphatase activity the presence of a high thymol turbidity titer and a strongly positive cephalin flocculation test indicate that there was diffuse involvement of the liver rather than obstruction of the extrahepatic biliary system The prothrombin deficiency and the failure of vitamin K to lower the prothrombin time also supports this view The history as well as the macrocytosis suggests that the hepatic involvement was not of such recent onset as the course of the final episode of severe jaundice might suggest In view of the fact that this patient also had albuminuria fever with a moderate leukocytosis and a cutaneous eruption the following possibilities should be considered

Infectious hepatitis or homologous serum jaundice Weil s disease

Acute toxic necrosis of the liver possibly due to arsenic or some other toxic agent

Cirrhosis of the liver with a final exacerbation producing the picture of so called galloping cirrhosis

The duration of the illness leading up to the final episode of jaundice is against infectious hepatitis and there was no history of possible contact with human blood products The fever is compatible with this diagnosis but a leukocytosis and macrocytosis would be unusual—particularly the latter unless there was some basic liver disease of longer standing as well *Spider angiomas* are not necessarily indic

ative of cirrhosis of the liver They may appear in pregnancy or in any disease associated with disturbed liver function including acute infectious hepatitis so that their presence is not of diagnostic value in this case

There is no history here of possible exposure to the causative agent of Weil s disease and no organisms were found in the urine The marked albuminuria which pointed to this possibility is not uncommonly seen in severe jaundice and this syndrome is often referred to as *bile nephrosis*

The fever leukocytosis profound intoxication and deep jaundice suggest the possibility of extensive suppuration There are many features compatible with a suppurative pylephlebitis in which coalescing abscesses are present due to infected thrombi in the portal system The vague abdominal pain may have resulted from some gastrointestinal infection which led to the formation of septic thrombi The long period of symptoms before the final acute phase of the illness is against this diagnosis

In view of the abdominal pain and the previous history of jaundice the possibility of obstruction of the common duct must be mentioned The severity of the hepatic insufficiency in the face of a normal phosphatase level seems to rule out this diagnosis

A toxic hepatitis must be considered There was no history of arsenic or phosphorus ingestion or of exposures to any other drugs known to produce liver damage The skin eruption and the renal changes might have been due to sulfonamide intoxication but there is no concrete evidence that the patient received a sulfonamide Jaundice can also result from a hypersensitivity reaction but it does not seem possible that this could be the whole explanation of such rapidly advancing liver insufficiency

It seems most likely that this patient had long standing hepatic involvement associated with chronic alcoholism and the dietary disturbances which accompany this addiction The episode of previous jaundice might thus be explained and the final illness would represent so called galloping cirrhosis The latter may be associated with fever and leukocytosis The hemorrhagic phenomena undoubtedly resulted from the prothrombin deficit But to account for the gastrointestinal bleeding a leaking varix or possibly a peptic ulcer may have been present Peptic ulcer apparently occurs more often in patients with liver cirrhosis than one would expect from mere coincidence It seems likely that the hemorrhages were a factor in precipitating the final rapid advance into hepatic coma

The reflex and other neurological changes are difficult to interpret Peripheral neuritis on a dietary basis might account for the diminished deep reflexes The other changes may have been accompaniments of hepatic coma or possibly associated with intracranial hemorrhage Hepatic coma is frequently accompanied by bizarre neurological manifestations

ANATOMICAL DIAGNOSIS (Autopsy No 21062) History of chronic alcoholism massive fat infiltration of liver with slight periportal scarring Jaundice Ascites Hydrothorax right Congestive splenomegaly Bile casts and fatty degeneration kidney tubules (bile nephrosis) Varices esophagus and stomach Chronic cholecystitis and cholelithiasis Fat necroses pancreas Calcified primary tuberculous nodule apex of left lung and hilar node caseous tubercles cervical nodes Aspiration pneumonia Hyperplasia femoral marrow Pheochromocytoma adrenal (small)

The large size of the heart was due to epicardial fat The liver was deeply bile stained and an indefinite pattern was made out suggesting lobulations rather than nodules The gallbladder was slightly thickened and edematous and contained a few dark faceted stones The spleen was enlarged Microscopically the liver cells were so loaded with fat that only a rim of cells was recognizable about the portal areas There was no true cirrhosis The lobules were intact and at most there was slight periportal scarring About the portal areas bile canaliculi were dilated with bile casts evidently produced by those few remaining periportal cells but no bile extravasation was seen and no necrosis of liver cells found The splenomegaly and varices were presumably due to portal obstruction but from the microscopic evidence no scarring sufficient to distort hepatic lobulation and produce portal obstruction could be seen nor was there any lesion in the main portal system The pathogenesis of the hepatic failure was on the basis of replacement of cytoplasm by fat There was no extramedullary blood formation in the spleen as is usual in the macrocytic anemia that results from such a lesion as this As a result of the jaundice there was renal injury typical of bile nephrosis The fever was probably due to the aspiration pneumonia

SUMMARY This 41 year old white female a chronic alcoholic had jaundice at age 26 Six months before death she developed anorexia loss of weight and vague epigastric pains Examination revealed an obese deeply jaundiced woman in coma with ecchymoses spider angiomas and hepatomegaly There was a leukocytosis macrocytosis and slight anemia prothrombin deficiency azotemia serum bilirubin of 43 mg % and only slight elevation of alkaline phosphatase activity These findings indicated that the jaundice was due to diffuse hepatic disease and a diagnosis of rapidly progressive cirrhosis with necrosis of liver cells was made Autopsy revealed MASSIVE FATTY INFILTRATION OF THE LIVER WITH SLIGHT PERIPORTAL SCARRING but no cellular necrosis

II

(#325827 Admitted July 4 1944 Died July 13 1944)

THIS 54-year old iron worker complained of swelling pain in the right upper quadrant and jaundice of ten days duration There had been occasional vague epigastric distress following meals in the past He had eaten poorly for a number of years and drunk a moderate amount of beer with some whiskey each day

He felt well until two weeks prior to admission when he developed a cough with some sputum which was blood streaked on several occasions Ten days before admission he developed a sense of fullness in the right upper quadrant with a dull pain increased by cough and deep inspiration The pain did not radiate Seven days before admission he developed intermittent attacks of hiccuping Five days before jaundice appeared which deepened progressively He complained of anorexia the urine became dark in color he had eight to ten stools a day and vomited on numerous occasions There was a history of exposure to rats There was no history of exposure to drugs

PHYSICAL EXAMINATION on admission T 101 P 120 R 25 B P 120/66

The patient was deeply jaundiced and had lost weight There was no lymph node enlargement The percussion note was unchanged There were bronchovesicular breath sounds over the right apex anteriorly with tubular breathing and numerous moist rales high in the right axillary region The heart was normal The abdomen was protuberant A soft tender liver edge was palpable 4 fingerbreadths below the costal margin in the anterior axillary line There was no splenomegaly or ascites or muscular tenderness Over the legs were numerous purpuric spots and a fairly large hemorrhage was seen in the right conjunctiva

COURSE IN THE HOSPITAL The patient continued to run fever the temperature at times reaching 103 He was given penicillin and for four days sulfamerazine The diarrhea increased in severity the last few days of his life In the beginning all of the stools were said to be acholic but the day before death the stools had a normal brown color During the last few days of life there was decrease in the bilirubinemia Despite adequate fluid intake progressive azotemia developed Generalized edema appeared with ascites On July 10 a diffuse maculopapular rash developed principally over the trunk and continued to spread The signs of consolidation in the lung increased The patient became comatose before death

LABORATORY DATA Hemoglobin 14 gm hematocrit 42 icterus index over 100 sedimentation rate 0 leukocyte count ranged from 15 000

to 23 600 with 10% juvenile neutrophils 78% segmented neutrophils 10% lymphocytes and 2% monocytes

Stools were loose and milky in appearance at first later described as light brown in color examinations revealed no blood or parasites Urine was dark brown in color specific gravity 1 012 trace of albumin no uro bilinogen There were no leptospira on darkfield examination of urinary sediment

Blood serologic test for syphilis was negative Culture from the throat showed a heavy growth of Friedländer s bacillus Sputum examination showed type XVII pneumococcus by direct Quellung and type XIII was isolated from a mouse inoculated with sputum, blood cultures showed no growth

Blood nonprotein nitrogen was 76 on admission falling to 27 on July 6 and then rising steadily to 176 mg % chloride 93 mEq CO_2 21 6 mEq cholesterol 182 mg % phosphorus 3 7 mg % alkaline phosphatase activity 6 units total serum protein 4 81 gm % with 3 gm % albumin Bilirubin on admission was 24 8 mg % total with 12 9 mg direct the last determination on July 12 showed total 14 6 mg % direct reading 10 7 Blood calcium on July 10 was 6 4 mg % with phosphorus 12 5 mg % Agglutination tests for leptospira were negative on two occasions Prothrombin time was normal

X ray examinations of the chest on July 5 showed a dense well circum scribed area of infiltration in the right mid and upper lung fields probably due to a pneumonic process Aorta was slightly tortuous The left lung was clear

DISCUSSION The striking features of this acute illness which ended a little over 3 weeks later in death were—signs of pulmonary consolidation jaundice with an enlarged tender liver and renal in sufficiency with azotemia At first glance it seems probable that either a septicemia due to an organism such as a staphylococcus anaerobic streptococcus or Friedländer s bacillus or a leptospiral infection might explain all of the facts

In bacteremia due to the anaerobic streptococcus or to the staphylo coccus metastatic abscesses may occur in almost any location One might in this instance suspect the lungs as the primary source of the infection but under the circumstances it would be most unusual not to find one of the above mentioned causative organisms in either the sputum examinations or in the blood cultures However, Friedländer s bacillus was discovered in the throat culture This organism is found not infrequently in the nose and throat of healthy individuals but bacteremia occasionally occurs with the lungs as the portal of entry The course of the resulting illness is acute with high fever, and vomit ing and diarrhea may be prominent symptoms Metastatic abscesses occur in the liver and kidneys, and maculopapular skin eruptions

have been described as well as petechial lesions However one would expect no difficulties in growing the organism from the blood stream In a *bacteremia* it would be unusual for the multiple liver and kidney abscesses to dominate the clinical picture to the degree present in this case As a rule the manifestations which they produce are inconspicuous in comparison with the general symptoms of sepsis

Weil s disease is characterized by fever conjunctival congestion pains in the muscles jaundice hemorrhagic diathesis and albuminuria Pneumonic consolidation may occur Muscle pains were conspicuously absent in this case and no agglutinins against the leptospiral organisms developed These cases may or may not respond to penicillin so that this is not a helpful point No organism could be seen on darkfield examination of the urine at a time when they might have been present but no guinea pig inoculation was done

It seems more likely that this disease cannot be explained on a single etiologic basis From the description the pulmonary findings are compatible with an acute pneumonic process and if pneumococci were found in large numbers they were probably the etiologic agent The skin eruption and the relationship of the azotemia to the administration of sulfamerazine strongly suggest that the renal damage was due to this drug

The major problem is the nature of the jaundice which had the characteristics of the regurgitation type with acholic stools bilirubinuria and largely direct reacting blood bilirubin It could have resulted from either necrosis of liver cells or from obstruction of the bile ducts With severe jaundice at the stage at which this man was seen clinical observations are most important as extensive parenchymatous damage to the liver will have taken place even if the primary factor was obstruction of the common bile duct and reliance on such tests as cephalin flocculation or thymol turbidity alkaline phosphatase levels etc will too often be misleading

Difficult to evaluate is the evidence of infection with fever and high leukocyte count with shift to the left This may have been due entirely to the pulmonary process or in part to infection in the liver or biliary tract

Under these circumstances with rapid development of severe jaundice of the regurgitation type one may suggest three possible explanations

(1) Acute necrosis of the liver cells perhaps in a previously cirrhotic or fatty liver The evidence of severe intoxication could have been the result of acute hepatic necrosis with insufficiency but it may

have been due to infection alone In those cases of jaundice due to widespread necrosis secondary to some infection, the jaundice usually appears later in the illness than it did in this case The liver is usually not as enlarged or as tender as in this instance, and pain is infrequent

(2) The fever marked leukocytosis profound intoxication and deep jaundice suggest the possibility of extensive suppuration This may be brought about by several causes, such as abscesses in association with general sepsis which have already been considered Solitary abscesses such as those caused by amebic infection seldom run a rapidly fatal course and intense jaundice is unusual This patient had diarrhea but no blood was present in the stools and no parasites were seen on two examinations

This illness is compatible with a suppurative pylephlebitis in which coalescing abscesses are present due to infected thrombi in the portal system There are high fever leukocytosis profound intoxication and often deep jaundice The illness runs a rapid course with death in two or three weeks In men the gastrointestinal tract is the usual source of such an infection and acute appendicitis is the usual primary disease There was nothing here to suggest disease of the gastrointestinal tract before the onset of the jaundice

(3) One must always be highly suspicious in cases of severe regurgitation jaundice of the possibility of *obstruction of the common bile duct by calculi* Although there was no preceding history of jaundice or of attacks suggesting acute biliary colic there was a story of vague epigastric distress after meals and prior to onset of the jaundice a sensation of fullness in the right upper quadrant accompanied by a dull pain Although the most characteristic feature of chronic cholecystic disease is the recurrence of attacks of biliary colic the symptoms may vary within wide limits At one extreme are those instances in which gallstones are found at autopsy in subjects who had no complaints referable to the biliary tract and at the other extreme are patients with severe biliary colic who at operation have a minimum of pathologic change in the gallbladder Epigastric fullness after meals with eructation is extremely common and may be the only manifestation of cholecystic disease until a stone lodges in the common duct

Fluctuating jaundice and the presence of pain are highly suggestive of obstruction of the common duct by calculi The liver was described as soft and there is the possibility that an enlarged gallbladder was palpated although this is uncommon in chronic cholecystic disease in contrast to its frequency in external obstruction such as that caused by carcinoma of the head of the pancreas The persistently

high leukocyte count the persistent tenderness enlargement and apparent softness of the liver and the rapid subsidence of the severe jaundice in the last few days of life suggest that the patient had common duct obstruction with empyema of the gallbladder

The persistent diarrhea was a prominent feature Bacterial cultures showed no pathogenic organisms and no parasites were present There was no blood in the stools Perhaps there was pancreatic involvement due to partial obstruction of the pancreatic duct as well

The terminal ascites and subcutaneous edema were probably associated with the renal insufficiency Some abdominal fluid may accumulate following pancreatic necrosis

Leakage of bile into the general peritoneal cavity is rare because the activity of the omentum usually prevents such an occurrence but it is conceivable that the terminal reduction in the degree of jaundice and the rather sudden appearance of bile in the stools may have been associated with the development of a communication between the biliary system and the colon However it is more likely that the patient passed a common duct stone

ANATOMICAL DIAGNOSIS (Autopsy No 19041) Early Laennec s cirrhosis with diffuse fatty infiltration of liver Chronic cholecystitis Cholelithiasis Stones in lumen and wall of gallbladder and in cystic duct with occlusion and in hepatic ducts Dilatation of hepatic and common bile ducts Jaundice Early biliary cirrhosis Foci of acute and chronic pancreatitis and fat necroses Bile casts in renal tubules Foci of extramedullary blood formation spleen Organizing and resolving lobar pneumonia right upper lobe with extension into adjacent portions of right middle and lower lobes Organizing serofibrinous pleurisy right Acute splenic tumor History of sulfonamide therapy and anuria Sulfonamide crystals in renal tubules and pelves Diffuse sulfonamide nephritis Dilatation of proximal convoluted tubules of kidneys Hydropic change of renal epithelium Fibrinous pericarditis Subacute enteritis with many eosinophils jejunum Aberrant pancreas in wall of jejunum Chronic bronchitis Foci of squamous metaplasia and calcification and ossification with bone marrow formation branch of the right main bronchus

The gallbladder was contracted and thick walled At the apex there were fragments of calculus embedded in the wall In the hepatic ducts there were numerous stones 4–5 mm in diameter and the ducts were dilated measuring 12 mm in circumference The hepatic and common ducts were dilated the latter measuring 25 mm The pancreatic duct was dilated The cholelithiasis was responsible for the major part of this patient s symptomatology but other complicating lesions were present Probably the abdominal pain was caused by a stone at the ampulla leaving the residual dilatation of the common bile duct This and other stones producing long standing obstruction were probably responsible for the focal pancreatitis

which was present and gave rise to periportal inflammatory lesions and early biliary cirrhosis The liver however was also the seat of an early but definite Laennec cirrhosis and a diffuse fatty infiltration of the liver cells suggested continuing injury so that this may have intensified the jaundice Lobar pneumonia partially resolved and with areas of organization was present in the right lung Bile casts were present in the kidneys but it was the massive tubular and interstitial sulfonamide nephritis that was responsible for the anuria There were many dilated tubules and in addition the epithelium was extensively altered by hydropic degeneration Sulfonamide crystals were seen in some collecting tubules This had caused damage to the renal epithelium and had given rise to an area of inflammatory reaction containing numerous eosinophils At one spot particularly the renal epithelium was penetrated and heaped up by an underlying reaction typical of a sulfonamide mechanical nephrosis

SUMMARY This 54 year old white man had a story of postprandial distress for many years Three weeks before death he developed fever cough bloody sputum fullness in the right upper quadrant with pain accentuated by cough and respiration and in a few days icterus and diarrhea Examination revealed jaundice pulmonary consolidation and a tender liver After sulfonamide therapy he developed an eruption and progressive azotemia but the icterus decreased Laboratory studies showed leukocytosis and evidence of severe obstructive jaundice with only slight elevation of alkaline phosphatase activity Stools at first were acholic and later had a light brown color It was decided that the patient had pneumonia and in addition nephritis as a result of the sulfonamide therapy The previous story of epigastric distress the tender liver in the presence of severe regurgitation jaundice and the apparent improvement in icterus with appearance of bile in the stools led to a diagnosis of BILIARY CALCULI In addition to these findings there was early PORTAL CIRRHOSIS with diffuse fatty infiltration of the liver and foci of acute and chronic pancreatitis It is noteworthy that in the presence of diffuse liver involvement the alkaline phosphatase activity did not rise as a result of the biliary duct obstruction

III

(#378231 Admitted March 8 1946 Died April 17 1946)

THIS 53 year old Negro female was admitted because of jaundice and epigastric pain of four weeks duration In April 1930 a left salpingectomy and oophorectomy had been performed and a dermoid cyst of the right ovary enucleated At that time the liver was palpable and there was tenderness on palpation over the gallbladder There was no history of any gastrointestinal symptoms or intake of alcohol

Nine weeks before admission the patient developed anorexia nausea vomiting and epigastric discomfort described as a sense of fullness and heartburn This lasted for one day and during the next three weeks she felt well except for two mild recurrences of the same symptoms Six weeks before admission these attacks increased in frequency and two weeks later became so severe that she went to bed She noted then that her urine was dark and the following day her scleras were jaundiced Shortly after this the stools became light in color A few days before admission she developed bleeding of the gums

PHYSICAL EXAMINATION on admission T 99 P 84 R 20 B P 130/90

The patient was obese and deeply jaundiced No spider angiomas were seen The eyes were normal The thyroid was not enlarged or tender There was no enlargement of the lymph nodes The lungs were clear There was a systolic murmur at the apex There was no resistance on abdominal palpation but there was generalized tenderness greatest in the epigastrium and right upper quadrant The liver edge was felt 7 finger breadths below the costal margin The spleen was not palpable there was no edema of the extremities and the reflexes were normal

COURSE IN THE HOSPITAL The patient ran a low grade fever and complained frequently of nausea The spleen was palpated on numerous occasions There was increasing distention and the mental status became cloudy Because of the possibility of obstruction of the biliary duct an operation was performed The patient died on the 10th postoperative day

LABORATORY DATA Red blood cells 4 66 million hemoglobin 15 3 gm hematocrit 47 8 mean corpuscular volume 102 mean corpuscular hemoglobin concentration 32 icterus index over 100 leukocyte count 5 150 with 5% juvenile neutrophils 59% segmented neutrophils 2% eosinophils 1% basophils 25% lymphocytes and 8% monocytes Serologic test for syphilis was negative Blood nonprotein nitrogen was 35 mg % sugar 94 mg % bilirubin total 27 8 mg % direct reacting 15 4 mg %

total serum cholesterol 315 mg % total serum protein 7 56 gm % with 3 63 gm % albumin

Stool examination on admission showed no bile but from March 18 to death bile was present in moderate amounts Urine had a specific gravity of 1 020 with 30 white cells per high power field no red cells or casts no sugar or albumin bile 4 plus urobilinogen not present

Further tests to establish the type of jaundice showed alkaline phosphatase activity 4 7 units cephalin flocculation 4 plus clotting time 14 minutes bleeding time 2 minutes prothrombin time 20 minutes (control 16 minutes) bromsulfalein test of liver function showed 69% retention in 45 minutes Just before death the serum bilirubin had risen to 32 4 mg % with 17 4 mg % direct

X ray film of abdomen on March 9 showed no gallstones or kidney stones A gastrointestinal series on March 11 showed normal esophagus stomach and duodenal bulb

DISCUSSION (Information about the operative findings was not made available to the discusser) The problem is to determine the cause of the jaundice Almost certainly there was extensive damage to the liver cells but its nature was not clear and the question arises as to whether it resulted from long standing partial obstruction of the extrahepatic bile ducts or from some primary disease of the liver

In long standing jaundice many of the criteria which are used in the clinical differentiation of biliary tract obstruction from intrahepatic disease are not helpful According to the data of Gutman and Hanger the diagnosis of common duct obstruction is highly improbable if the serum alkaline phosphatase level is below 10 and the cephalin flocculation test is strongly positive Such was the case here but Gutman and Hanger s tests failed to indicate common duct obstruction in almost 25 per cent of the cases of proved choledocholithiasis Regardless of the results of the laboratory tests the diagnosis in this case should explain the severe persistent jaundice with hepatomegaly and the evidence of diffuse hepatocellular damage in the absence of acceptable clinical evidence of portal obstruction

Portal cirrhosis as the sole hepatic lesion seems readily eliminated This condition rarely causes massive liver enlargement and severe jaundice in the absence of portal obstruction Possibly there was an early cirrhosis with a superimposed primary neoplasm of the liver As an explanation for the recurrent attacks of epigastric discomfort biliary obstruction by neoplastic cells seems unlikely Subacute liver necrosis superimposed on portal cirrhosis would not ordinarily be accompanied by such evident hepatomegaly

The course of this disease and its isolated occurrence in a 53 year old woman would be against a diagnosis of infectious hepatitis How

ever one must consider further the possibility of cirrhosis following a prolonged hepatitis Watson Hoffbauer and Howard have de scribed what they call the *cholangiolitic type of hypertrophic cirrhosis* with a clinical picture characterized by pruritus jaundice without ascites enlarged liver and spleen hypercholesterolemia and hyper phosphatasemia Obviously this is not the syndrome presented by this patient

Occasionally Hodgkin s disease predominantly involves the liver The splenomegaly suggested this possibility Hodgkin s disease is rare in the absence of other lymphatic involvement but is difficult to rule out Intra abdominal node enlargement might contribute to the jaun dice by pressure on the common bile duct The same may be said for hepatic sarcoidosis which may produce the syndrome of portal obstruction

There was no history of exposure to any hepatotoxic agent

The recurrent attacks of indigestion together with the finding many years previously of right upper quadrant tenderness and a questionably palpable liver suggest that this woman had long stand ing biliary tract disease and a chronic biliary cirrhosis The final severe jaundice may have been precipitated by intermittent duct ob struction by stone The evidence of mild infection and the intermittent attacks of epigastric pain and so called indigestion could thus be explained This patient had bile in the stools after the first few days in the hospital so it does not seem likely that there was persistence of a stone in the common duct

The nature of the pain in this case although not typical suggests the possibility of carcinoma of the pancreas Pain appears in about 50 per cent of these cases although the association of painless jaun dice with pancreatic carcinoma is stressed in most textbooks The jaundice also may be intermittent and fluctuating rather than steadily progressive One striking manifestation of pancreatic carcinoma was not present—the rapid loss of weight Other common features such as a palpable gallbladder were also absent Furthermore to explain the liver involvement one would have to assume diffuse metastatic lesions which rarely cause such extreme reduction in liver function as this patient exhibited

The final choice seems to fall between a persistent severe infectious hepatitis with cirrhotic changes and chronic biliary tract disease with a biliary cirrhosis and cholelithiasis In view of the rapidly progressive course after jaundice developed the absence of typical signs of gall bladder disease the enlargement of the spleen and the normal leuko

cyte count the first possibility is the more likely one particularly in view of the postoperative course Patients with diffuse liver damage due to infectious hepatitis are often made much worse by operation under a general anesthetic Death in cholemia may result

ANATOMICAL DIAGNOSIS (Autopsy No 19897) Subacute widespread necroses of liver with great proliferation of smaller bile ducts Jaundice, ascites Bile casts both kidneys History of exploratory laparotomy and cholecystostomy Cholelithiasis Lobular pneumonia Acute splenic tumor Pulmonary edema bilateral Arteriosclerosis aorta and coronary and intrarenal arteries Calcified primary tuberculous complex left Scars at both lung apices Metaplasia pancreatic ducts with scarring chronic inflammation and fat necrosis Chronic thyroiditis marked

The liver was greatly reduced in size Its capsule showed irregular areas of wrinkling resembling pigskin On section the wrinkled areas conformed to collapsed brown tissue with concentrated portal spaces suggesting complete loss of hepatic tissue Other areas showed mottled green tissue with a swollen consistency suggesting areas of regeneration The hepatic and common ducts were normal Microscopically the liver showed widespread necrosis of the cells and there were whole fields in which no liver cells could be found There was marked proliferation of the bile ducts in the periportal areas Other sections showed remaining islands of liver cells There was marked metaplasia of the epithelium of the pancreatic ducts with foci of fat necrosis areas of atrophy and scarring resulting from obstruction The thyroid showed scarring and lymphoid infiltration There were foci of Hurthle cells

SUMMARY This 53 year old Negro female had anorexia vomiting and epigastric discomfort for five weeks and then ten weeks before death developed icterus Examination revealed fever obesity deep jaundice marked hepatomegaly and enlargement of the spleen There was a macrocytosis without anemia evidence of regurgitation jaundice and normal alkaline phosphatase activity The patient died ten days postoperatively In view of the rapidly progressive course the absence of typical signs of gallbladder disease the splenomegaly and the normal leukocyte count a diagnosis of chronic infectious hepatitis was made Autopsy showed SUBACUTE NECROSIS OF THE LIVER This organ was very small in contrast to the clinical impression It is possible that the liver decreased in size while the patient was in the hospital

IV

(#172556 Admitted March 9 1947 Died March 18 1947)

This 80-year old white female complained of nausea vomiting abdominal swelling and jaundice She had diabetes mellitus treated with insulin for 6 years before admission

She had had ill defined gastrointestinal complaints for many years and occasional episodes of nausea and vomiting 3 years previously Four weeks before admission she developed pain across the upper abdomen radiating to the flanks She also complained of shooting precordial pains and palpitation with slight exertional dyspnea Increasing weakness and constipation developed with bowel movements every second or third day Two weeks befroe adn ssion she lost her appetite and began to vomit frequently *immediately after meals There was little nausea and no hematemesis* She recognized no retained food in the vomitus Her abdomen became prominent and one week before admission jaundice was noticed The urine became dark but the stools did not change in color The patient lost 20 pounds in weight the month before admission

Physical Examination on admission T 100 2 P 100 R 16 B P 140/60

The patient looked chronically ill and was icteric The skin was loose The retinal vessels showed moderate arteriosclerosis There were moist rales at both lung bases with diminution of breath sounds at the right base There was a soft apical systolic murmur The abdomen was distended and there was shifting dullness but no fluid wave A mass which had a hard nodular edge was palpable in the right hypochondrium extending across the abdomen to the left mid clavicular line A tender firm nodule 3 cm in diameter was felt in the gallbladder area Rectal examination showed external hemorrhoids but no masses There was edema of the ankles The ankle jerks were absent

Course in the Hospital During the first few days the patient ran a low grade fever After regulation of her diabetes a laparotomy was performed When the peritoneal cavity was entered clear yellow fluid *escaped The liver appeared normal on the surface* A tremendously enlarged gallbladder was evident Exploration of the liver spleen stomach bowel pelvis and pancreatic regions revealed no evidence of disease Some stones were evacuated from the gallbladder Following this the common duct was exposed and it was not dilated or inflamed The distal 2 to 3 cm was not seen The neck of the gallbladder was full of small stones and seemed to be compressing the common hepatic duct just supe

rior to the cystic duct There seemed to be on initial palpation a small stone in the common duct distal to the cystic duct A small catheter was passed into the common hepatic duct No obstruction or stone was met The catheter was then passed into the distal portion of the common duct for a distance of about 3 inches It was thought to be in the duodenum but saline irrigation into the catheter came back into the wound A soft probe was passed easily into the duodenum The gallbladder was removed The patient died postoperatively after developing signs of pneumonitis The jaundice had not improved

LABORATORY DATA Blood serologic test for syphilis negative hemo globin 13 gm hematocrit 42 icterus index greater than 100 sedimentation rate 38 mm per hour leukocyte count 9 000 with normal differential count The stool was light brown soft and test for blood was negative Urine was dark amber with specific gravity 1 030 sugar 2 plus albumin 1 plus occasional red cell and white cell per high power field bile 4 plus urobilinogen positive in 1 to 80 dilution Bilirubin total 17 6 mg % direct reacting 12 1 Alkaline phosphatase activity 17 8 units Cephalin floccula tion test negative Thymol turbidity 1 3 units Prothrombin time 19 seconds 65% of normal Serum amylase 450 reducing units

X ray examinations gastrointestinal series on March 10 1947 showed normal esophagus stomach and duodenum A barium enema on March 13 1947 revealed no organic lesion

DISCUSSION This 80 year old woman had a history of vague gastrointestinal complaints before the final illness One month before admission she developed anorexia vomiting upper abdominal pain loss of weight distention ascites and jaundice There was a low grade fever but no acute attacks of pain and no intermittency of the jaundice The gastrointestinal series revealed no lesion and at opera tion there was cholecystitis with cholelithiasis but the common duct was not dilated The head of the pancreas felt firm but palpation of the organs in the area revealed no evidence of neoplasm

The striking feature was the jaundice which seems a reasonable starting point for analysis of this case

(1) The jaundice was progressive and associated with vague upper abdominal pain and ascites

(2) The urine contained large amounts of bilirubin and little uro bilinogen

(3) The stools were light brown in color and contained no blood

(4) The major portion of the serum bilirubin gave a direct reaction on the van den Bergh test

(5) The cephalin flocculation and thymol turbidity tests were nor mal while the alkaline phosphatase activity of the serum was ele vated

These findings point not only to a regurgitation type of jaundice but to one associated with biliary duct obstruction Both the distention of the gallbladder and the ascites associated with evidence of biliary duct obstruction suggest neoplasm as a possibility Common duct stone is rarely accompanied by ascites while peritoneal metastasis or vascular obstruction from a tumor may readily result in the accumulation of free fluid in the peritoneal cavity As the common duct was not dilated the enlargement of the gallbladder may have been due to a small stone in its neck or in the cystic duct

However these findings leave one with some doubt that cholelithiasis was the primary factor in this case and before it is assumed that the findings at operation were the complete answer further possibilities must be considered particularly as the jaundice failed to improve

As the biliary tree was carefully explored with the exception of the final 3 cm which could not be exposed let us list the possible lesions in this area

(1) Stone lodged at the ampulla of Vater
(2) Carcinoma of the pancreas
(3) Chronic pancreatitis
(4) Metastatic nodes or duodenal diverticulum producing compression
(5) Carcinoma of the common duct ampulla of Vater or duodenum

It is difficult at times to be certain even at operation of a stone near the ampulla However apart from the reasons already advanced this seems unlikely in the absence of previous attacks of biliary colic or jaundice the gradual and progressive character of this illness without intermittency of symptoms and the ready passage of a soft probe down the duct into the duodenum

Obstructive jaundice with enlargement of the gallbladder developing in a patient of this age always suggests carcinoma of the pancreas However the jaundice is most often painless and palpation by an experienced surgeon can usually detect the neoplasm

That pancreatitis was present seems likely from the elevated serum amylase This might also have been a factor in the production of the pain However in view of the degree of jaundice it seems most likely that the pancreatitis was secondary to the bile duct obstruction and not the primary disease

Enlarged lymph nodes may have caused biliary obstruction in this

case but there is no evidence to indicate a primary disease of the lymphatic system and the x ray and surgical examinations failed to disclose a primary source for metastases

It seems reasonable to assume from this analysis that this was a very small lesion difficult to detect and so strategically placed that it could produce a rapidly fatal illness

The cholecystitis and cholelithiasis do not account satisfactorily for the entire picture The only other lesion by exclusion which could have escaped detection and produced pancreatitis and obstructive jaundice is a neoplasm of the ampulla of Vater or the adjacent portion of the duodenum or less likely a small duodenal diverticulum The ascites could be accounted for by peritoneal implants or associated with pancreatitis and fat necroses

Anatomical Diagnosis (Autopsy No 20492) Adenocarcinoma of ampulla of Vater with extension to pancreas with lymphatic invasion and metastases to regional lymph nodes common duct liver, duodenum stomach pancreas gallbladder diaphragm peritoneum adrenals and kidney *Widespread necroses both adrenals Pancreatic duct and acinar* dilatation Fat necroses pancreas Biliary cirrhosis History of cholecystectomy and common duct exploration Hemorrhagic and necrotic liver Pulmonary emboli Aspiration pneumonia and pulmonary edema Fibrinopurulent pleurisy Hydropic degeneration of kidneys Coronary and generalized arteriosclerosis Myocardial scars Calcified foci in lungs and hilar nodes Hemorrhagic cystitis Endometrial polyp

The tissues at the hilum of the liver were distorted by tumor The common duct was unstained with bile and was compressed by masses of tumor some lying in the lymph nodes which involved the tissue at the hilum The tumor had seeded itself on the peritoneal surface This was a typical adenocarcinoma which arose from the mucosa of the ampulla of Vater and invaded the lymphatics in diffuse fashion both in the mucosa and throughout the wall of the duodenum There were widespread metastases but these were mostly microscopic in size hence the failure to recognize them at operation In the adrenal there were larger lymphatic tumor masses with resulting thrombosis of adrenal vessels and widespread areas of fresh adrenal necrosis The metastases in the liver were intralymphatic in character There was widespread periportal scarring with bile duct proliferation and typical biliary cirrhosis In the pancreas there was dilatation of the large duct from obstruction by the tumor and even in the tail of the pancreas numerous foci of dilated acini were seen as well as recent fat necrosis It is interesting that although the tumor at the ampulla could account for the entire clinical picture at operation stones were also found and metastases had compressed the bile duct at the hilum As the duct was not bile stained or dilated this latter lesion was probably the major one in the production of the jaundice The probe at operation probably passed through the soft tumor into the duodenum

The only way to be certain of a lesion in this area is to open the duodenum for direct visualization

SUMMARY This 80 year old woman had anorexia vomiting upper abdominal pain loss of weight abdominal distention ascites and jaundice The jaundice was severe and progressive the urine contained large amounts of bile the serum bilirubin was direct reacting the cephalin flocculation and thymol turbidity tests were normal and alkaline phosphatase activity was elevated This indicated common duct obstruction and at operation she had cholelithiasis The common duct was not dilated and a probe entered the duodenum without difficulty The jaundice did not improve and she died of postoperative pneumonia This suggested a lesion strategically placed in the last three centimeters of the common duct The presence of ascites suggested tumor in addition to gallstone Accordingly a diagnosis of CARCINOMA OF THE AMPULLA OF VATER was made This was found at autopsy but the jaundice was mainly due to obstruction by metastases compressing the common duct

V

(#236296 Admitted January 22 1948 Died January 25 1948)

THIS 42 year old white man had a total of six admissions to the hospital In 1940 he had nervousness and anorexia which increased, and he developed severe nausea and vomiting with generalized abdominal pain There was *dimness of vision and numbness of the legs with tenderness in the* soles and calves On examination there was a retinitis with hemorrhages and possible optic neuritis Nothing was found to explain the abdominal complaints He lost weight but slowly improved In February 1942 he again developed nervousness weakness vomiting and pain in the epigastrium The pain came after meals and was crampy Vomiting produced some relief In June 1942 the abdominal symptoms became severe, the patient lost 17 lb in weight and was admitted for study

At that time temperature pulse and respiratory rate were normal blood pressure was 105/85 He was a pale emaciated nervous man who appeared tired Pupils reacted to light There were central scotomas Exudate was seen near the left optic disc The heart and lungs showed no abnormalities There was a firm tender smooth fixed mass situated superficially in the right upper quadrant just to the right of the midline *which did not move with respiration Bizarre sensory disturbances were* found in the legs and there was diminution of the deep tendon reflexes Laboratory examinations showed no anemia white count was normal with 5/ eosinophils Sedimentation rate was 34 mm per hour and urine was normal X ray of the abdomen showed numerous stippled calcified bodies just to the right of the second lumbar vertebra thought to be in the head of the pancreas

He continued to have gnawing pain more severe after meals He was re admitted in October 1942 with the same findings Laboratory studies showed alkaline phosphatase activity 17 2 units and normal bromsulfalein excretion Abdominal exploration was done October 28 1942 A mass was found in the region of the head and first part of the body of the pancreas Biopsy showed chronic inflammation and scarring of peripancreatic tissue

The patient continued to have abdominal pain *nausea flatulence* and vomiting Examination in October 1944 showed no change other than extreme emaciation The hard mass was still palpable

On at least one occasion he had a transient episode of jaundice The abdominal pain persisted and he particularly noted its onset after eating fatty foods *In December 1947 he began drinking heavily and developed* frequent vomiting During this period his food intake was low His abdom

inal pain was more severe Five days before the final admission he became jaundiced his stools were frequent and foul smelling and his urine dark Morphine was necessary for relief of pain Three days before admission profuse sweating and delirium developed

Physical Examination on admission T 99 P 100 R 36 B P 120/75

The patient was cachetic disoriented deeply jaundiced and hiccuping constantly Spider angiomas were noted and there was palmar erythema The pupils were dilated but reacted to light There was no lymph node enlargement The lungs were clear The heart was not enlarged The abdomen was full and moved with respiration To the right of the midline in the epigastrium there was a large tender firm irregular mass Above the mass a smooth moderately firm liver edge was felt There was no ascites or splenomegaly The deep tendon reflexes could not be elicited

Course in the Hospital There was no improvement and large amounts of sugar were excreted in the urine The jaundice decreased but the patient became comatose and died two days after admission

Laboratory Data Blood serologic test for syphilis was negative red cells 3 15 *million* hemoglobin 11 gm hematocrit 34 mean corpus cular volume 106 icterus index 100 sedimentation rate 26 mm per hour leukocyte count 5 200 with 5% juvenile neutrophils 58% segmented neutrophils 20% lymphocytes 7% monocytes

Stools were brown and contained no occult blood specific gravity of the urine was 1 030 with sugar 4 plus albumin 2 plus and occasional bile stained epithelial cells

Blood chemical examinations showed chloride 85 7 mEq CO_2 24 6 mEq sugar 290 mg % calcium 8 2 mg % phosphorus 2 7 mg % alkaline phosphatase activity 33 7 units cholesterol 132 mg % bilirubin total 16 *mg % direct reacting 10 6 prothrombin time 26 seconds 50% of normal* serum amylase 250 mg reducing substance *serum proteins 5 5 gm %* thymol turbidity 11 9 cephalin flocculation 3 plus

X ray film of the abdomen showed multiple calculi throughout the pancreas

Discussion The course of this illness was a chronic one the patient having been an invalid for 8 years The pain often precipi tated by ingestion of fatty food the cachexia the abdominal inflam matory mass the x ray evidence of pancreatic calculi the development of symptoms of pancreatic insufficiency (diarrhea with foul stools) and the diabetes mellitus all are characteristic features of that syn drome of unknown etiology—*calcareous pancreatitis* During one attack there was moderate elevation of the serum amylase These patients often become chronic alcoholics as did this patient The frequent leakage of pancreatic juice with digestion of vessel walls by trypsin leads to the formation of an *inflammatory mass such as this* patient had There may be chronic partial biliary duct obstruction leading to diffuse hepatic disease and periodic episodes of jaundice

There seems little doubt about the presence of chronic calcareous pancreatitis but it seems desirable to examine more closely some of the other features of the final illness During an alcoholic spree the patient went without food developed protracted vomiting had a return of severe abdominal pain and became delirious and deeply jaundiced There were spider angiomas and the palms were erythematous The jaundice seems to have been obstructive in type, as the van den Bergh reaction was largely direct and the alkaline phosphatase activity extremely high the stools light brown in color with bile stained epithelial cells in the urine In addition, there was evidence of hepatic cellular damage with elevation of the thymol turbidity reaction positive cephalin flocculation test, and a macrocytic type of anemia He may have had a portal type of cirrhosis unassociated specifically with his pancreatic disease but developing in association with alcoholism and poor food intake The final alcoholic spree with starvation may have precipitated a rapid and extensive destruction of liver cells producing a picture of subacute yellow atrophy Against that is the clinical impression that the jaundice decreased considerably before death This observation was not confirmed by chemical tests but if correct is in favor of the jaundice being mainly the result of a common duct obstruction which was suddenly relieved Indeed if the change was as dramatic as the notes indicate there may have been rupture of the biliary tree with leakage of bile into some portion of the peritoneal cavity or the intestinal tract

Since the final picture was compatible with death due to cholemia, one must consider other possible causes of destruction of liver tissue There was no known exposure to any hepatotoxic agent Although the patient had had chronic pancreatic disease for many years a neoplasm may have developed a carcinoma of the pancreas with liver metastases or even a primary liver tumor in a setting of portal cirrhosis Both of these seem unlikely in view of the apparent rapid clearing of the jaundice

The prominent features of the final illness which must be accounted for are (1) the pain was more intense than ever before (2) the jaundice was great but cleared significantly and (3) the alkaline phosphatase was extremely high The last of these might be associated with bone metastases but in view of the jaundice it suggests an acute biliary tract obstruction A stone lodged in the common duct could explain all of these features Infection with abscess formation may be a complication of calcareous pancreatitis but the absence of fever the

normal leukocyte count, and the apparent rapid improvement are less well explained than by postulation of a common duct stone

ANATOMICAL DIAGNOSIS (Autopsy No 21030) Chronic pancreatitis with massive scarring pancreatic calculi and multiple pancreatic and peri pancreatic abscesses (*Escherichia coli* and gram positive cocci) Dilated bile ducts Acute and chronic cholecystitis Acute cholangitis with portal abscesses Biliary cirrhosis Jaundice Penetration of duodenal wall by abscess Acute duodenal ulceration Acute perigastritis Perinephric scar ring and abscess Tubular degeneration of adrenals Chronic splenic tumor Lobular pneumonia History of diabetes mellitus Lesion of Armanni renal tubules Focal necrosis hypophysis Pulmonary thrombi containing foreign bodies (? cotton fibers) Gynecomastia Atrophy partial both optic nerves

At the junction with the splenic vein the portal vein overlay an abscess cavity and its wall was infected by extension There was a series of multi locular abscesses about the head of the pancreas involving the head itself There was a great deal of scarring and numerous calculi were seen in the ducts There was dilatation of the duct toward the tail and here too were abscess cavities and scarring The spleen was enlarged Doubtless the nausea anorexia and epigastric pain for many years were related to his severe pancreatic disease Microscopic sections showed the organ almost completely destroyed by dense fibrous scar tissue dilated ducts filled with calcium and purulent exudate Innumerable abscesses studded the pancreas and penetrated the capsule Abscesses thus lay adjacent to the duodenum stomach spleen and left kidney but generalized peritonitis did not occur The gallbladder showed both chronic and acute inflammation The liver revealed the effects of both obstruction and infection Dilated bile ducts were present in all periportal regions as well as marked proliferation of bile ducts and periportal scarring Abscesses were present in the periportal regions as well as plugging of dilated ducts by leukocytes The severe infection with marked change in the adrenals may have accounted for the failure of fever and leukocytosis to develop

SUMMARY This 42 year old white man had for eight years had recur rent epigastric pain weight loss and development of an inflammatory abdominal mass Numerous calcareous deposits were seen in the pancreas During an alcoholic bout he developed protracted vomiting diarrhea delirium and deep jaundice Spider angiomas macrocytosis elevated thymol turbidity and positive cephalin flocculation suggested diffuse hepatic damage The high alkaline phosphatase and the clinical improve ment in jaundice pointed to common duct obstruction The absence of fever and the normal leukocyte count favored common duct stone rather than infection and abscess formation around the pancreas Autopsy dis closed infection with abscess formation superimposed on a CHRONIC CALCAREOUS PANCREATITIS The infection had extended into the biliary tree and other surrounding structures thus accounting for the severe jaundice and fatal termination

VI

(#149002 Admitted May 18 1951 Died May 18 1951)

THIS 69 year old white female was admitted because of jaundice and coma In 1940 she had been seen complaining of recurrent epigastric pains Since the age of 13 she had had a chronic dyspepsia and had been unable to eat certain foods without experiencing abdominal pain and eructation In 1937 she had two attacks of sharp colicky pain in the right upper quadrant radiating through to the back which had lasted 2 to 3 days On two occasions she had transient periods of jaundice and with one attack the stool had been clay-colored She stated that she had always been rather nervous

On physical examination in 1940 the blood pressure was 180/100 and mild vascular changes were seen in the retinas She was not icteric The liver edge was palpable on deep inspiration and there was tenderness over the gallbladder On gallbladder x rays the dye did not enter the gallbladder The gastrointestinal series done at that time showed a diverticulum arising from the anterior and medial aspect of the second portion of the duodenum

In February 1941 cholecystectomy was performed and a large stone was removed from the common duct just distal to the cystic duct She continued to have some abdominal discomfort however particularly after eating excessive amounts of food She had hypertension on several visits with pressure up to 200/120 In December 1946 after a good many dietary indiscretions and after having been constipated for several days she developed a severe pain across the lower part of the back which lasted approximately 2 weeks This cleared up and her bowels began to move regularly but the pain reappeared 2 or 3 weeks later and she had constant severe pain in the right upper quadrant No jaundice was noted Examination at that time revealed tenderness along the upper border of the abdominal incision and a small hernia was found which was assumed to be the cause of her difficulties She was seen in the Accident Room in 1949 with another attack of abdominal pain which had begun 4 days previously following a heavy meal She had severe cramping epigastric and right upper quadrant pain which radiated through to the back Temperature and white count were normal at that time The hemoglobin was 14 gm She was said to have been acutely distressed On examination the abdomen was tense and there was slight spasm in the right upper quadrant and epigastrium with no rebound tenderness The liver edge was just palpable She was not jaundiced

She was then lost sight of until her final admission The patient was

unresponsive and the history was taken from her husband who stated that in December 1950 he noticed that his wife s eyes were yellow She was having frequent attacks of abdominal pain with no nausea vomiting or anorexia Two days before admission she became quite anorexic after eating cucumbers She vomited repeatedly and her jaundice appeared to deepen

Physical Examination on admission T 101 6 P 112 B P 80/50

The patient was unresponsive and was noted to be jaundiced Her skin was cold and clammy She was dehydrated and very cyanotic Pupils were small but reacted to light No lymph node enlargement was noted A few scattered moist rales were heard throughout the lung fields Heart was slightly enlarged and a systolic murmur was present The abdomen was distended and tympanitic There was generalized tenderness with rebound tenderness No bowel sounds could be heard Reflexes were normal

Course in the Hospital The patient was given intravenous fluids placed on antibiotic therapy and transfu ed In spite of oxygen her cyanosis *did not improve the blood pressure did not rise significantly She died* within a few hours after admission to the hospital

Laboratory Data Serologic test for syphilis was negative Hemoglobin was 14 gm leukocyte count 10 000 Urine showed 5 white cells per high power field and a positive foam test for bile Blood nonprotein nitrogen was 54 mg / chlorides 90 4 mEq phosphorus 2 5 mg / CO_2 34 3 mEq total serum protein 4 7 with 3 1 gm albumin bilirubin total 8 0 mg % direct 6 2 mg % alkaline phosphatase activity 6 9 cephalin flocculation 3 plus thymol turbidity 3 2 amylase 423 reducing units potassium 2 5 mEq /L

The electrocardiogram showed normal sinus rhythm Levogram T waves were biphasic in leads one and two

X ray examination of the abdomen showed the psoas and renal shadows were obscured Some air was present in the stomach Air was also present in small intestinal loops and in the large intestine On the upright film there was no definite evidence of any fluid level

Discussion *This is an interesting problem* as it brings out many important points in the interpretation of pain occurring in a patient with known biliary tract disease First of all this 69 year old woman *had been having gastrointestinal symptoms with attacks of abdom*inal pain since the age of 13 During her late 50 s a diagnosis of gall bladder colic was made and a common duct stone was removed at operation An x ray of the gastrointestinal tract showed a duodenal diverticulum After operation she was seen on several occasions with abdominal pain often radiating to the back but not accompanied by jaundice Approximately *six months before death she was noted to* be jaundiced and had abdominal pains during all of this period Two days before admission she developed nausea and vomiting and

became more jaundiced and comatose She had fever, hypotension cold and cyanotic extremities abdominal distention with tenderness In spite of transfusions she died a short time after admission

On first consideration it would seem difficult to explain this entire series of events on the basis of a single diagnosis Her final illness was severe and rapidly fatal Could this have been due to rupture of the biliary system with bile peritonitis or intestinal obstruction due to a large stone? Could the duodenal diverticulum which was described play some role in this picture or was the final episode something entirely different such as a vascular accident associated with her known hypertension?

It seems desirable first to come to some decision about the jaundice It was said to have been present for several months continuously the bilirubin determinations and the positive foam test for bile in the urine suggest regurgitation jaundice Again the chemical tests are difficult to interpret The cephalin flocculation test was strongly positive and the alkaline phosphatase was only doubtfully elevated This I believe does not mean that she had diffuse liver disease without obstruction to the common bile duct because in long standing bile duct obstruction there may be a chronic biliary cirrhosis so that the supply of alkaline phosphatase is greatly reduced and the expected elevation does not occur

Considering now the nature of the final acute episode with vomiting shock and death in 2 days—the more likely explanations would seem to be internal hemorrhage acute peritonitis acute intestinal obstruction and acute pancreatitis The first of these seems highly improbable in view of the lack of evidence of bleeding from the gastrointestinal tract and the hemoglobin of 14 gm Peritonitis due to perforation of the bowel possibly into the lesser peritoneal sac, bile peritonitis or peritonitis secondary to leakage of pancreatic juice all have to be considered Persistent vomiting and the rapid downhill progress suggest intestinal obstruction at a high level There were no fluid levels in the upright abdominal film but a large amount of gas was present in the stomach The sudden severe and rapidly fatal illness the terminal collapse the prior attacks of upper abdominal pain the low grade continuous jaundice and the moderate elevation of blood amylase all suggest pancreatitis Most of the evidence seems to direct our attention to the common duct the pancreatic duct and the duodenum The possible explanations of the picture seem to be

(1) Common duct stone with perforation of the biliary duct or with obstruction of the pancreatic duct

(2) Stricture of common duct
(3) Chronic calcareous pancreatitis with obstruction of both com mon and pancreatic ducts
(4) A narrow necked duodenal diverticulum with retention of food, enlargement inflammation obstruction of biliary and pancreatic ducts and possibly terminal intestinal obstruction or perforation

The chronicity and mildness of the jaundice are points against common duct stone Neither a stone nor a stricture would adequately account for the terminal events unless complicated by a perforation of the duct

It seems to me that duodenal diverticulum with food impaction obstruction inflammation and pressure on the pancreatic and com mon bile ducts and a terminal acute pancreatitis or intestinal per foration or obstruction would best explain the course of events Duodenal diverticula are not uncommon being seen in about 2 per cent of gastrointestinal x rays but they rarely produce symptoms When they do the symptoms may closely simulate gallbladder colic or the pain of pancreatitis The patients usually have recurrent gas trointestinal complaints over a period of many years as did this patient—from the age of 13 This could account for the attacks of pain without jaundice subsequent to the operation It is of interest that in two cases reported in the literature the patients had had gall bladder operations without relief of symptoms In each case subse quent operation revealed a duodenal diverticulum containing gall stones

The only case I have seen in which a duodenal diverticulum caused trouble was a 38 year old woman who had had indigestion for 3 years jaundice for 3 months and pain in the abdomen and back for 4 days Examination showed coma jaundice low blood pressure a distended abdomen with a little ascites and a greatly enlarged liver There was a diverticulum just below the ampulla of Vater pancrea titis with fat necrosis and a huge liver filled with fat I believe that with possible minor variations this will be essentially the situation in the case today

Anatomical Diagnosis (Autopsy No 23035) History of cholecys tectomy 10 years previously and recurrent bouts biliary colic since that time Duodenal diverticula one adjacent to ampulla of Vater Cholangio lithiasis with dilated bile ducts and main pancreatic ducts Small abscesses in liver Infected thrombi in small branches of portal vein Early biliary cirrhosis Focal necroses liver Tubular degeneration of adrenals Chronic cystitis and pyelonephritic scars Generalized arteriosclerosis Narrowing

of both renal artery orifices by arteriosclerosis Small right renal artery Hypoplasia of right kidney History of hypertension Patchy atelectasis and edema of lungs

The heart was enlarged and the left ventricle hypertrophied The lungs were wet and dark red in color The liver was bile stained The ducts were greatly dilated measuring up to 15 mm in diameter These formed huge cavernous channels throughout the central portion of the liver but were not nearly so prominent near the periphery Despite the green color the liver appeared quite fatty The extrahepatic bile duct was dilated tremendously with a circumference of 52 mm The wall of the duct was thickened and there was scarring in places Removed from this huge dilated duct were a number of stones which had a soft greenish exudate on the surface but the internal surface of the stones was typical of bilirubin-cholesterol stones There were two large duodenal diverticula which measured about 2 cm at their ostia and extended about 3 cm in length There was a smaller diverticulum immediately adjacent to the ampulla and just above it This diverticulum was about 1 cm deep and clearly could press upon the terminal portion of the bile duct when distended Immediately above it the duct was greatly dilated It seemed probable that the dilatation of the duct and the formation of the gallstones were partly due to this diverticulum There are numerous similar cases in the literature with duodenal diverticulum near the ampulla stones and biliary cirrhosis Interestingly many of these are in elderly people suggesting that atonicity of the intestine may lead to overfilling of such diverticula The terminal event in the present case was ascending infection There was purulent cholangitis with small abscesses and infected thrombi in veins in the periportal region The circulatory collapse was probably due to septicemia and the antibiotic therapy may have accounted for the sterile blood cultures at autopsy The large pancreatic ducts were also dilated There was no pancreatitis and the symptoms appear to have been produced by the biliary tract disease alone although the serum amylase activity was moderately elevated

SUMMARY This 69 year-old woman had had attacks of dyspepsia and abdominal pain since the age of 13 When examined at age 60 a diagnosis of gallbladder colic was made and she had had two transient attacks of jaundice X ray of the gastrointestinal tract showed a duodenal diverticulum A common duct stone was removed at operation She continued to have attacks of abdominal pain without jaundice Six months before admission she developed jaundice and the attacks of pain continued Two days before entry she developed nausea and vomiting the jaundice deepened and she became comatose Examination revealed fever hypertension cyanotic extremities abdominal distention with tenderness Total serum bilirubin was 8 mg % alkaline phosphatase activity only slightly elevated cephalin flocculation 3 plus and serum amylase 423 units The long history of gastrointestinal symptoms and the evidence of diffuse hepatic disease in a patient known to have had cholelithiasis suggested that the duodenal diverticulum might have played a part in partially impeding or intermittently obstructing the flow of bile The pain may in part have been the result of intermittent pancreatic duct obstruction as

suggested by the elevation of serum amylase activity At autopsy there was cholangiolithiasis with dilatation of the biliary ducts and main pancreatic ducts and early biliary cirrhosis A DUODENAL DIVERTICULUM was found near the ampulla of Vater The terminal illness was the result of an ascending infection of the biliary tract

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Chapter 8

HEPATOMEGALY AND ASCITES

Hepatomegaly

WHEN A MASS is felt in the right upper abdomen or epigas trium one should not jump too hastily to the conclusion that it is an enlarged or displaced liver Tumors of the stomach transverse colon or right kidney may simulate hepatomegaly A thickened omentum such as occurs in chronic tuberculous peritonitis or fecal masses in the transverse colon or a distended gallbladder may also be mistaken for liver In some individuals one can feel a tongue like projection of the liver—Riedel s lobe—which may be mistaken for an enlarged gallbladder A correct distinction between these various pos sibilities frequently depends upon care and skill in palpation and a thorough understanding of the anatomical factors involved When a mass is palpated every accessible portion of its margin should be felt It is often helpful to trace the outline of the mass on the abdomen with a skin pencil and then to attempt to plot its anatomical relation ships in a diagram

The liver may be palpable without being actually enlarged It is frequently felt in normal children up to the age of about seven years In adults it may be felt when it is displaced downward by depression of the diaphragm as in pulmonary emphysema by subdiaphragmatic abscess or as a result of laxness of the supporting tissues In some adults with thin abdominal walls a liver of normal size may be felt at the height of a deep inspiration Additional information concern ing the size of the liver may be obtained by percussing both the upper and the lower border and by x ray examination

The configuration and consistency of an enlarged liver are always worthy of note When the enlargement is diffuse the liver edge is usually felt most readily in the right hypochondrium lateral to the

thick rectus muscle Occasionally the enlargement may involve the left lobe and may be mistaken for an enlarged spleen If the enlargement is irregular and gross nodules can be felt metastatic disease is probable The cirrhotic liver if enlarged is usually not grossly irregular to the palpating hand characteristically it has a firm sharp edge In contrast with this the liver of chronic passive congestion does not usually present a well defined edge even when its anterior surface can be felt with ease

Once it has been determined that the liver is enlarged information concerning the cause of the enlargement may be obtained by investigating the extent of dysfunction of the parenchymal cells the reticuloendothelial system and the biliary collecting tree Tests designed to provide such information are discussed in greater detail in the section on jaundice There is of course no correlation between the size of the liver and the degree of functional disturbance In the study of these cases the recording of a careful history is essential Particular attention should be paid to possible exposure to injurious chemical agents to the presence of factors which might impair the circulation the diet possible exposure to infectious agents or a family predisposition to hepatic disease Important also is the search for evidences of hypertension in the portal circulation the presence of jaundice spider angiomas and anemia Pain is not often a prominent feature but local discomfort of varying intensity may presumably be ascribed to distention of the liver capsule Discomfort in the right shoulder in some cases results from irritation of the portion of the diaphragm supplied by the phrenic nerve Localized tenderness may sometimes be detected over a liver abscess Table 11 presents a simplified classification of the conditions in which enlargement of the liver may occur In the presence of various states associated with venous congestion of the liver this organ is usually enlarged in a uniform and regular fashion Massive liver enlargement as a result of heart failure may be noted in some cases of mitral stenosis it is seen particularly in patients with constrictive pericarditis and the hepatomegaly may be so prominent that the liver is thought to be the seat of intrinsic disease If the tricuspid valve is incompetent the liver may pulsate Care must be taken not to mistake for hepatic pulsation the downward thrust of the liver caused by contraction of a hypertrophied heart By placing one hand on the front and the other on the back of the abdomen over the liver the two hands can be felt to be separated by an expansile pulsation

In cases of obstruction of the common duct the degree of hepatic

Table 11 Causes of Hepatomegaly

I Venous congestion of the liver
  A Congestive heart failure
  B Obstruction of the vena cava or hepatic veins by
    1 Tumor
    2 Thrombosis
II Obstruction of the common bile duct
  A Gallstone
  B Pancreatitis
  C Neoplasms of pancreas ampulla bile ducts
  D External pressure of various types including duodenal diverticulum
III Infection
  A Localized abscess formation
    1 Amebic
    2 Anaerobic streptococcus
    3 Associated with pylephlebitis
  B Infectious hepatitis and homologous serum jaundice
  C Spirochetal jaundice
  D Amebic hepatitis
  E Syphilis
  F Tuberculosis
  G Actinomycosis
  H Brucellosis
  I Hydatid cyst
IV Diffuse hepatomegaly without infection
  A Cirrhosis of the liver
    1 Portal cirrhosis
    2 Biliary cirrhosis
  B Toxic hepatitis
  C Amyloid disease
  D Hemochromatosis
  E Sarcoidosis
  F Other metabolic defects including von Gierke s disease lipoidosis Wilson s disease
V Neoplasm
  A Lymphoma and leukemia
  B Metastatic carcinoma and sarcoma
  C Primary tumors

enlargement depends upon the severity and persistence of the process Here again the liver is palpably smooth and regular Whether the obstruction is due to a gallstone to pancreatitis or to neoplasm there will of course be jaundice of the obstructive type

Localized abscess formation in the liver may be due to an amebic infection even though there have been no gastrointestinal manifesta

nostic sign In the days before modern surgery ovarian cysts sometimes reached tremendous size and were not infrequently mistaken for ascitic accumulation Even today ovarian cysts are occasionally punctured by a trocar inserted for the purpose of removing ascitic fluid The recovery of thick viscid brownish or greenish material typical of the contents of ovarian cysts, may be the first indication of the true cause of the abdominal distention Suspicion of an ovarian cyst should be aroused when the enlargement of the abdomen is asymmetrical and when the flanks do not bulge and are tympanitic to percussion Although hydramnios may at times give many of the physical signs of ascites the true nature of the condition is usually made evident by the history and by the findings on pelvic examination If serious doubt remains resort may be made to one of the pregnancy tests It is not generally realized that in acute dilatation the stomach may occasionally reach such proportions as to virtually fill the abdominal cavity In a case which recently came to autopsy all that could be seen through the pathologist s long midline incision was a huge fluid filled sac which proved to be a dilated stomach In this case a diagnosis of ascites had been made prior to death Such great dilatation of the stomach is usually encountered in debilitated elderly individuals but we have observed it in a young women with lobar pneumonia and in another young woman with severe and protracted pleurodynia There may be no gastric symptoms The condition can be correctly diagnosed by passing a tube into the stomach The atony of the distended stomach is usually so great that fluid can be removed only by applying continuous suction to the tube

When ascites occurs alone without other evidence of disturbed water balance or when it is the first evidence of such disturbance it may serve quite satisfactorily to orient the consideration of differential diagnosis On the other hand its value as an avenue of approach to diagnosis is limited when it is only one of many evidences of water retention If it is merely part of a generalized edema in which the *face is involved, then renal disease or hypoproteinemia is the most* likely cause In some cases of diffuse hepatic disease hypoproteinemia may lead to edema formation before portal obstruction is far enough advanced to cause ascites If ascites is preceded by the development of edema confined to the legs and other dependent areas it is probably due to heart failure

When ascites is the sole or outstanding clinical feature, three types of disease must receive first consideration (1) tuberculous perito-

nitis, (2) cirrhosis of the liver (3) tumor metastases involving the peritoneal surfaces Abdominal paracentesis early in the course of the diagnostic study of such cases serves many useful purposes The ascitic fluid may be examined to determine whether it is a transudate

Table 12 Causes of Ascites

I Infection of the peritoneal cavity
- A Secondary to rupture of a hollow viscus
  - 1 Appendicitis
  - 2 Peptic ulcer
  - 3 Diverticulitis
  - 4 Empyema of the gallbladder
- B Tuberculosis

II Venous obstruction
- A Portal vein obstruction secondary to diffuse hepatic disease
  - 1 Portal cirrhosis
  - 2 Hepar lobatum
- B Portal vein thrombosis
  - 1 Invasion by neoplastic disease
  - 2 In chronically ill patients
- C External pressure on the portal vein
  - 1 Tuberculous lymph nodes
  - 2 Lymphoma
  - 3 Malignant tumors
  - 4 Sarcoidosis
- D Obstruction of inferior vena cava above the hepatic vein
  - 1 Thrombosis
  - 2 Mediastinal mass
- E Cardiac disease with chronic elevation of venous pressure
  - 1 Mitral stenosis
  - 2 Chronic right heart failure due to other causes
  - 3 Constrictive pericarditis

III Lymphatic obstruction with chylous ascites

IV Secondary to tumor implantations on the peritoneum (carcinoma of tail of pancreas)

V Bile peritonitis

VI Hemoperitoneum

or an exudate or whether it is chylous in character Microscopic and cultural studies may be made for tubercle bacilli and other bacteria The centrifuged sediment may be examined for tumor cells More over after the ascitic fluid has been withdrawn there is an oppor tunity for much more satisfactory abdominal palpation and pelvic

examination The finding of an enlarged liver previously masked by ascites allows one to survey the diseases known to cause both hepato megaly and ascites The presence of tumor masses in the abdominal cavity or pelvis immediately suggests tuberculous peritonitis or ma lignant tumor Age is a factor to be taken into consideration here Tuberculous peritonitis is the most frequent cause of ascites in chil dren Effusions due to tumor metastases occur most often in the older age groups

Fever and abdominal pain and tenderness are usually present in tuberculous peritonitis There may also be evidence of tuberculosis in the lungs or elsewhere In some cases fever and other evidences of infection may be absent In women with ascites and a pelvic mass the distinction between tumor and tuberculosis may be impossible with out exploratory laparotomy

When ascites is due to portal obstruction from cirrhosis of the liver there may be evidence of collateral circulation hematemeses melena spider angiomas splenomegaly jaundice hypoalbuminemia, and impairment of liver function The liver may or may not be en larged depending on the state of the disease and the type of treatment that the patient has received

Ascites due to tumor impl ints usually occurs in patients over 40 years of age There may be enlargement of the liver due to metas tases The primary tumor is usually situated in the gastrointestinal tract or in the body or tail of the pancreas Tumors of ovarian origin should be thought of in women When the primary tumor cannot be located ascites due to metastatic peritoneal implants may be difficult to distinguish from that due to tuberculous peritonitis or hepatic cirrhosis If the ascitic fluid is bloody or chylous it suggests a neo plastic origin

In most instances it is not difficult to make the diagnosis of acute peritonitis due to rupture of a hollow viscus The sudden onset of pain manifestations of infection and the signs of peritoneal irrita tion ordinarily furnish abundant evidence An x ray picture of the ab domen taken in the upright position may show air beneath the dia phragm In certain instances when there is only slight leakage from an almost completely walled off perforation of an appendix a peptic ulcer a Meckel diverticulum or a typhoid ulcer a large accumulation of free fluid may develop in the peritoneal cavity without producing significant clinical signs of peritonitis This is particularly true in elderly individuals in whom the constitutional signs of infection as

well as the evidences of preceding gastrointestinal disease may be negligible Obstruction of the portal vein in the absence of liver disease is usually due to lymphoma or metastatic tumor involving the periportal lymph nodes Coincident obstruction of the common bile duct is frequent leading to progressive jaundice Primary thrombosis of the portal vein is rare It may follow compression or invasion of the vein by a malignant tumor Infected thrombi may extend into the vein from an acutely inflamed appendix or other inflammatory process When the portal vein is obstructed splenomegaly is almost always sufficient to be readily detectable

Ascites due to obstruction of the inferior vena cava above the level of entrance of the hepatic veins is usually the result of some mediastinal mass or chronic mediastinal infection Evidence of intrathoracic disease may furnish the clue to the correct diagnosis In most cases in which cardiac disease leads to ascites there are other evidences of heart failure However such signs may not be evident in cases of constrictive pericarditis In these cases there is in addition to ascites hepatic impairment of a significant degree These findings may lead to a mistaken diagnosis of cirrhosis of the liver Since constrictive pericarditis is amenable to surgical treatment it should never be overlooked as a possible cause of ascites and hepatomegaly The venous pressure should be determined in the arms and if it is elevated other diagnostic procedures including cardiac fluoroscopy and the various *types of kymography should be carried out*

Bile peritonitis may be due to rupture of the gallbladder or bile ducts secondary to trauma calculi tumors or other diseases It may also be caused by inadvertent injury to the bile ducts during surgical operations In recent years several cases of bile peritonitis have been reported following needle biopsies of the liver

Hemoperitoneum is usually due to trauma Rupture of the liver or spleen is the most common source of the hemorrhage Intra abdominal hemorrhage may also be associated with rupture of an extra uterine pregnancy Spontaneous rupture of the spleen with massive hemoperitoneum has been reported in cases of malaria True aneurysms and dissecting aneurysms of the abdominal aorta or its major branches usually rupture into the retroperitoneal tissues In some cases however the rupture may occur directly into the peritoneal cavity or there may be a secondary rupture from the retroperitoneal spaces into the peritoneum Hemoperitoneum may also occur following surgical operations upon the intra abdominal or pelvic organs

In cases of hemorrhage the rapidity of development of the signs of peritonitis depends of course, upon the size of the blood vessels involved and upon the adequacy of the clotting mechanism There are usually evidences of acute peritoneal irritation Seepage of blood from the peritoneal cavity into the subcutaneous tissues of the abdominal wall is sometimes heralded by the appearance of ecchymotic patches The bluish discoloration surrounding the umbilicus in cases of ruptured extrauterine pregnancy is known as Cullen s sign

Illustrative Cases

I

(Albany Hospital #B 56469 Final admission October 7 1953 Died October 13 1953)

THIS 52 year old Italian laborer was first admitted to the Albany Hospital in July 1953 complaining of palpitation which had first been noted one year previously with an attack lasting several hours There was associated weakness and sweating but no chest pain cough or vomiting Subsequently he suffered two similar episodes There was no history of iron therapy blood transfusion or alcoholism Other details of family and past history were not available

PHYSICAL EXAMINATION on first admission T 98 P 65 R 20 B P 120/70

The patient was cheerful and comfortable The heart was not enlarged Rhythm was regular and a systolic murmur of moderate intensity could be heard over the entire precordium Lungs were normal On palpation the liver was firm and smooth and extended almost to the iliac crest Spleen was also firm and extended 4 cm below the left costal margin Small axillary and inguinal nodes were noted

LABORATORY DATA Serologic tests for syphilis were negative Erythrocytes were 4 0 million hemoglobin 9 5 gm hematocrit 32 leukocytes 3 100 with 55% neutrophils 2% eosinophils 42% lymphocytes and 1% monocytes A blood smear showed some target cells anisocytosis poikilocytosis and marked hypochromia The urine contained a trace of albumin no sugar a few white cells and an occasional red cell Fasting blood sugar was 108 mg % nonprotein nitrogen 37 mg % total serum protein was 8 1 gm % with 3 8 gm % of albumin and 4 3 gm % of globulin Total bilirubin was 3 4 mg % *direct reacting 0 3 mg % Bromsulfalein retention* was 64% in 45 minutes Total serum cholesterol was 80 mg % of which 74% was cholesterol esters Cephalin flocculation was 2 plus in 24 hours 4 plus in 48 hours

X ray picture of the chest was normal A gastrointestinal series was negative but the films showed enlargement of the liver and spleen and some calcification thought to be in the capsule of the spleen Barium enema was negative except for calcified bodies below the liver thought to be gallstones Intravenous urograms were not well delineated but dis

closed no abnormalities The sternal marrow aspirate revealed marked erythrocytic hyperplasia hemosiderin was abundant in the stroma and in the macrophages A needle biopsy of the liver was performed (the findings were not disclosed to the discusser) Platelets in the circulating blood 634 000 per cu mm Reticulocytes were 1% A fragility test gave hemolysis beginning at 0 42% and incomplete at 0 20% saline Hemolysis of control blood began at 0 44% and was complete at 0 32% A direct Coombs test as well as a test for fetal hemoglobin was negative Stools gave a 1 plus benzidine reaction

SUBSEQUENT COURSE The patient was discharged on the 10th hospital day with no definite diagnosis He had no further attacks of palpitation felt well and returned to work Two and one half months later he was admitted to the hospital after vomiting about a pint of blood and passing bright red stools This was the first evidence of hemorrhage

PHYSICAL EXAMINATION on second admission T 98 8 P 92 R 18 B P 116/80

The patient showed slight icterus There were no spider angiomas Cardiac rhythm was regular with a harsh systolic murmur heard both at the base and the apex Erythrocytes numbered 3 5 million hemoglobin was 6 0 gm

COURSE IN THE HOSPITAL On the morning after admission the patient vomited approximately 1 liter of bloody fluid and went into shock Whole blood transfusion was given, and a Blakemore tube was inserted into the esophagus Blood pressure rose to 118/70 On the third hospital day erythrocytes were 3 7 million and hemoglobin 10 5 gm Prothrombin time was 20 5 seconds (control 15 seconds) The Blakemore tube was removed on the following day and was replaced 48 hours later (on the 6th hospital day) when the patient again went into shock More blood was given by transfusion Following this the blood pressure returned temporarily to normal but the patient went into coma and fetor hepatis was noted Auricular fibrillation developed with a ventricular rate of 200 per minute This could not be controlled by Digilanid C Nonprotein nitrogen was 138 mg% creatinine 3 4 mg% potassium 4 1 mEq , sodium 146 mEq CO_2 23 mEq chlorides 113 mEq The patient died on the 7th hospital day

DISCUSSION This case affords an opportunity to discuss the differential diagnosis of both hepatomegaly and massive gastrointestinal hemorrhage but in addition to these major evidences of disease there are a number of other points of interest

Before going on to a discussion of some of the other factors I am going to make the assumption that the patient had *thalassemia minor* This diagnosis seems to afford the best explanation of one group of the findings It would account for

(1) hypochromic anemia with leptocytosis
(2) erythrocytic hypercellularity in the bone marrow
(3) splenomegaly

(4) hyperbilirubinemia,
(5) hemosiderosis,
(6) increased osmotic resistance of the red blood cells

A strong point in favor of this diagnosis is the patient s nationality In a survey in Rochester N Y , it was calculated that one out of every 25 individuals of Italian extraction living in that area had this trait so it is certainly a relatively common occurrence in Italian families

One synonym for thalassemia is Mediterranean anemia Although this disease has its greatest prevalence among the Mediterranean peo ple it is an interesting commentary that both forms of the disease were first accurately described in Italians and Greeks who had mi grated to the United States Thalassemia major was first described by Cooley and is sometimes called Cooley s anemia Thalassemia minor was first characterized by Wintrobe in 1941 The disease has now been recognized also in people of non Mediterranean origin Cooley s anemia is generally speaking a fatal disease of children and its pathological anatomy has been described in detail On the other hand thalassemia minor is a non fatal trait Very little has been written about its pathological anatomy In fact I have been unable to find records of complete autopsies on any of these patients

At this point it might be well to ask whether thalassemia could account for all the major findings in this case As far as possible we would like to explain the entire picture on the basis of a single dis ease I have already listed the findings which could certainly be ac counted for by thalassemia Additional major findings which we would like to explain are

(7) hepatomegaly
(8) hyperglobulinemia
(9) positive cephalin flocculation
(10) low serum cholesterol
(11) hypoprothrombinemia
(12) gastrointestinal hemorrhage
(13) nitrogen retention,
(14) coma

This entire list of items could be quite readily explained by a liver disturbance of the type seen in advanced cases of portal cirrhosis Does thalassemia minor ever lead to this type of cirrhosis? I have been unable to find reports indicating that it does However it is known that hemosiderosis following prolonged iron therapy or mul tiple blood transfusions may result in what is called secondary hemo

chromatosis Goldish and Aufderheide have reported a case of se ondary hemochromatosis in a patient with chronic hypochrom anemia closely simulating but not identical with thalassemia It w believed by the authors that the hemosiderosis in this case could n be accounted for by transfusions or iron therapy They ascribed t hemosiderosis to improper utilization of absorbed iron Their patie had a very large liver with cirrhosis and portal obstruction It is interest that there were even gallstones and calcification in the sple to simulate the findings in the present case

It might now be profitable to take the hepatomegalv as our poi of focus and give it more detailed consideration The most comm causes of hepatomegaly may be included under the following gener headings

(1) *Venous congestion* of which there was no evidence in this cas

(2) *Infection* such as acute hepatic pyogenic infections with lar or small liver abscesses amebic infections syphilis brucellosis, sch tosomiasis hydatid disease and others There was no fever in th case The liver was not tender The serologic test for syphilis w negative and in general there was virtually nothing to point towar an infectious process However subacute liver necrosis of the typ seen in some cases of infectious hepatitis may occur in the absenc of fever or other evidence of infection

(3) *Obstruction of the common bile duct* Although this patient ha gallstones there is certainly nothing to suggest the symptomatolog of common bile duct obstruction The type of jaundice and th hepatic functional disturbances were different from what one sees common duct obstruction

(4) *Diffuse hepatomegaly without obstruction of the common bil duct* Under this heading the following would be included

(a) *Portal cirrhosis* in which the liver is not usually greatly enlarge However in a small percentage of cases enlargement may be con siderable particularly if there is associated fatty infiltration Th usual story is that the liver is enlarged early in the disease and be comes smaller as the disease progresses This however, is not alway the case It has already been stated that the functional disturbance exhibited by this patient are consistent with the diagnosis of porta cirrhosis

(b) *Toxic hepatitis* This may be observed in certain types of poi soning There is no history of exposure to toxic substances in thi case

(c) *Amyloid disease*, in which case the liver may be quite large

It is usually firm and has a sharp edge I have been told that the biopsy of the liver did not show amyloid and we can dismiss this possibility without further discussion

(d) *Sarcoidosis* In this disease the liver is usually not greatly en larged although it may be palpable

(e) *Hemochromatosis* which has already been mentioned It is noteworthy that the portal cirrhosis of hemochromatosis frequently results in the production of considerable degrees of hepatomegaly The size of the liver in the present case is certainly compatible with this diagnosis

(5) *Neoplasms* These may be of three general types

(a) *Lymphoid deposits* either diffuse or nodular associated with either lymphoma or leukemia There was nothing to suggest that this patient had leukemia although abdominal Hodgkin s disease or lymphosarcoma cannot be readily excluded The lack of any signifi cant enlargement of lymph nodes and the evidence of hepatocellular damage are against these possibilities

(b) *Metastatic tumors* These usually cause an irregular nodular type of liver enlargement which was not present in this case

(c) *Primary tumors of the liver* These are prone to occur in livers which have previously been involved by cirrhosis They may be super imposed on the cirrhosis of hemochromatosis If this patient had a primary tumor I would suspect that it developed on the basis of a pre existing cirrhosis

Let us now take for consideration another of the major findings in this case the massive bleeding from the gastrointestinal tract Mas sive hemorrhages of this type are due to benign ulceration of the esophagus stomach or duodenum in more than 50% of the cases Hemorrhages from the upper gastrointestinal tract usually result in tarry stools However if the hemorrhage is sufficiently great bright red blood may be passed Since this patient vomited blood the site of the hemorrhage was probably above the level of the jejunum Taken in conjunction with the large liver there is every reason to believe that the hemorrhage came from dilated esophageal varices It is reported that such varices were not found in the x ray studies in spite of careful search This gives some reason for doubt but the x ray is not infallible in this regard A point in favor of a ruptured esophageal varix is the fact that the hemorrhage was controlled at least temporarily by the use of a Blakemore tube There is also the possibility that the bleeding may have been promoted by some fault in the blood clotting mechanism

If the patient had cirrhosis of the liver with portal obstruction why should he suddenly go into what was considered to be hepatic coma? I believe this may be attributed to the massive hemorrhage Progressive hepatic failure in cases of cirrhosis is sometimes greatly accelerated by hemorrhage Although it is possible that there was a superimposed acute necrosis this seems unlikely in the present case

The nitrogen retention may also have been a post hemorrhagic phenomenon This is a frequent occurrence when blood is retained in the gastrointestinal tract after a large hemorrhage One would also have to consider the possibility of a bile nephrosis—the so called hepatorenal syndrome—or a post transfusion lower nephron nephrosis Since there was little evidence of true renal failure I am inclined to believe that the nitrogen retention was due to retention of blood in the intestines

Some consideration must also be given to the condition of the heart The patient s first symptoms were those of rapid heart action and terminally he had auricular fibrillation The systolic murmurs of increasing intensity could be accounted for by the increasing anemia but in view of the arrhythmias one must consider the possibility of some type of myocardial disease In a man of this age arteriosclerotic heart disease would have to be given first consideration No electrocardiogram is recorded in the case abstract Information from this source might have been helpful In view of the large liver and spleen one must think also of the possibility of amyloidosis or sarcoidosis of the myocardium However considering the other findings in this case I am inclined to suspect that the heart muscle was the site of hemosiderin deposits Such deposits in the course of hemochromatosis frequently lead to rapidly progressive myocardial failure

Now to come to the diagnosis The following is offered

(1) Thalassemia minor
(2) Hemosiderosis secondary to thalassemia, involving multiple organs including the liver and the heart
(3) Portal cirrhosis of the liver secondary to hemosiderosis with portal obstruction
(4) Hemorrhage due to ruptured esophageal varix possibly aggravated by hypoprothrombinemia
(5) Cholelithiasis
(6) Possible primary carcinoma of the liver originating in a cirrhotic liver

When a diagnosis has been arrived at it is always desirable to scrutinize all of the evidence both positive and negative, in the light

of that diagnosis I have done this and I am reasonably satisfied with the results One may ask why it would not have been better to arrive at a diagnosis of primary hemochromatosis This also would have explained most of the findings quite satisfactorily I would like to point out however that no bronzing of the skin was mentioned in the case record and that there was no evidence of diabetes Although these are not necessarily present in all cases of primary hemochromatosis they are points against such a diagnosis A positive test for fetal hemoglobin might have been helpful in establishing the diagnosis of thalassemia A negative test however does not exclude this diagnosis The very low total serum cholesterol with a relatively high percentage of esters is somewhat disturbing These are not the characteristic changes in cirrhosis of the liver It is important to note, however that the cholesterol determination was not repeated We are therefore entitled to suspect a laboratory error However very low serum cholesterols may be encountered terminally in some cases of severe hepatic failure

ANATOMICAL DIAGNOSIS (Autopsy No A 53–333) Hemochromatosis advanced with marked involvement of the liver pancreas spleen kidneys prostate bone marrow and skin Cirrhosis of liver pigment type marked Varices of esophagus moderate Hemorrhage recent marked in the gastrointestinal tract Splenomegaly marked Icterus moderate of conjunctivas Bronchopneumonia acute of lower lobes Bronchitis and bronchiolitis acute Cystitis acute hemorrhagic Atherosclerosis slight of aorta and coronary arteries Perisplenitis chronic Adenoma islet cell of pancreas Cholelithiasis bile pigment type

The pathologist reported that the skin appeared to him to have a bronze tint The peritoneal cavity appeared normal except for the markedly enlarged liver and spleen Although the liver was not very nodular sectioning the greatly enlarged organ which weighed 4 120 grams showed it to be sclerosed and reddish brown in color Histologically it was the seat of advanced hemosiderosis with associated pigment cirrhosis The findings were characteristic of those observed in hemochromatosis Evidences of marked portal obstruction were also present The spleen (1270 grams) showed extreme congestion and the gastric and esophageal veins were markedly distended Although no bleeding point could be found in the lower portion of the esophagus the stomach was found to contain 400 ml of clotted blood and the source of hemorrhage was undoubtedly an esophageal varix The spleen pancreas kidneys bone marrow and skin were the site of marked hemosiderin deposits and hemofuscin was found in the stromal tissues of the pancreas Evidences of old chronic sclerosing pancreatitis with focal scarring sometimes involving the islets of Langerhans was also present Many of the islets some of which contained hemosiderin deposits were hypertrophied and a single large islet cell adenoma was present Little else was found in other organs except for the

terminal acute bronchopneumonia and acute hemorrhagic cystitis There were no positive findings which would permit the pathologist to make a diagnosis of thalassemia He concluded that the patient had primary hemochromatosis chiefly because of the characteristic changes in the organs including the pancreas and his ability to demonstrate hemofuscin as well as hemosiderin in the pancreatic tissue

SUMMARY A 52 year old Italian laborer who had blood and bone marrow findings consistent with thalassemia minor entered the hospital because of palpitation and was found to have hepatomegaly splenomegaly and mild jaundice Hemosiderosis was noted in material aspirated from the sternal marrow An x ray picture showed gallstones The patient improved and left the hospital without a definite diagnosis Two and one half months later he was readmitted following a large gastrointestinal hemorrhage and passed into what was considered to be hepatic coma Prior to death there were nitrogen retention and auricular fibrillation It was believed that all of the important findings could be explained on the basis of thalassemia minor with hemosiderosis pigment cirrhosis of the liver portal obstruction and hemorrhage from a ruptured esophageal varix It was postulated that the cardiac abnormalities might also be explained on the basis of hemosiderosis The findings at autopsy were interpreted by the pathologist as primary HEMOCHROMATOSIS The heart muscle was not involved in this process but there was coronary arterio sclerosis It still seems possible that the hemochromatosis was secondary to thalassemia although cases of this sort have not been previously reported in adults having only the thalassemia trait

NOTE This clinical pathological conference was held at the Albany Medical College May 6 1954 The clinical discussion was presented by one of us (JB III) and the autopsy findings were presented and discussed by Dr Arthur W Wright Since then an article on the occurrence of secondary hemochromatosis in an adult patient with thalassemia major has been reported by Curnn

II

(#417894 Admitted April 14 1947 Died April 26 1947)

THIS 40-year old metal burner entered complaining of swelling of the abdomen jaundice and weakness There was no history of previous icterus He had consumed large quantities of wine for 5 years but always ate well

In November 1946 he noticed that his trousers were too tight in the waist Shortly after this he noted the onset of episodes of vomiting after meals not accompanied by nausea or pain By January 1947 the abdomen was very swollen his appetite was poor and he was vomiting frequently In March he noticed jaundice His stools became clay colored and his urine dark During this period he lost 40 pounds in weight

PHYSICAL EXAMINATION on admission T 98 6 P 90 R 35 BP 110/60

The patient appeared very ill and was intensely jaundiced The abdomen was swollen which was in contrast to the emaciation noted elsewhere There was no generalized lymph node enlargement no abnormality on examination of the optic fundi and no papillary atrophy of the tongue There were a few rales at both lung bases The cardiovascular system was normal Marked ascites was present and after paracentesis a tender irregular liver edge was palpable 4 fingerbreadths below the costal margin The spleen was also palpable and superficial abdominal veins were visible but not prominent There was no edema The reflexes were normal

COURSE IN THE HOSPITAL The temperature was irregular during his days in the hospital at times reaching 101 6 The patient became disoriented progressively more drowsy and eventually stuporous Flat plate of the abdomen was normal

LABORATORY DATA Serologic test for syphilis negative red blood cells 4 7 million hemoglobin 12 gm leukocyte count 25 000 with 92% polymorphonuclears 6/ lymphocytes and 4% monocytes Urine had a specific gravity of 1 022 sugar and albumin 1 plus occasional granular cast bile 4 plus urobilinogen negative Stool was brown formed with 4 plus guaiac reaction Blood nonprotein nitrogen was 38 mg % chlorides 97 mEq CO_2 22 5 mEq serum protein 5 7 gm % with albumin 2 3 gm % phosphorus 4 2 mg / alkaline phosphatase activity 10 Bodansky units total serum bilirubin 40 mg % with 24 mg / direct reacting cholesterol 106 mg % thymol turbidity 9 units cephalin flocculation 4 plus prothrombin activity 30/ normal serum amylase 2747 mg % reducing substance Paracentesis was performed with removal of 2500 ml of bile stained fluid pH 7 5 specific gravity 1 008 125 mononuclear cells per cu mm culture no growth

DISCUSSION Many times in the diagnosis of a complicated case a reliable finding about which one can assemble the diagnostic pos sibilities is not evident Here there are three clear cut objective facts—ascites jaundice and hepatomegaly These several findings, coupled with the presence of splenomegaly greatly assist one in narrowing down the possible causes of this illness

Ignoring for the moment the results of the laboratory tests this illness would appear to be due to cirrhosis of the liver with painless ascites terminating in a rapidly progressive and extensive necrosis of liver cells The rapid progress and deep jaundice might also be ex plained by primary carcinoma of the liver superimposed on cirrhosis or by intercurrent infection

The character of the ascitic fluid the severe icterus the hepato megaly and the chemical pattern (positive cephalin flocculation in crease in thymol turbidity with alkaline phosphatase activity not greatly elevated) are consistent with portal obstruction complicated by diffuse hepatic damage The gradual onset of the ascites suggests that the portal obstruction was slow in development as may occur in progressive hepatic damage where there is simultaneous connective tissue proliferation and scar formation This sequence of events may occur in the course of a variety of diseases associated with jaundice and hepatomegaly

(1) Syphilis of the liver with gumma formation (hepar lobatum) rarely leads to severe hepatic insufficiency In an individual with a negative serologic test for syphilis and no history of antisyphilitic treatment this possibly may be dismissed

(2) Occasionally Hodgkin s disease produces enlargement of the liver and spleen This is rare in the absence of lymphatic involvement elsewhere

(3) The same may be said of sarcoidosis

(4) Secondary neoplastic disease even when extensive rarely produces such marked impairment of hepatocellular function It is sel dom associated with splenomegaly The intense jaundice would have to be explained on the basis of biliary duct pressure This explanation would not be consistent with the blood chemical pattern

For the most part the facts are in accord with progressive diffuse damage to the liver The course is rather rapid for ordinary portal cirrhosis although once ascites or jaundice has developed the life expectancy in these cases is not great Anorexia nausea and vomit ing may be prominent symptoms in patients with cirrhosis who have a terminal peritonitis with bacteremia and leukocytosis The consti

tutional manifestations of infection may also be seen with that form of acute necrosis of the liver sometimes called 'galloping cirrhosis

The level of the serum amylase seems too high to be explained on any basis other than an extensive pancreatic lesion In Opie s cases of pancreatitis about 25 per cent were associated with cirrhosis of the liver Recurrent attacks of pancreatitis might explain the vomiting but the absence of pain would be most unusual The development of severe acute pancreatic necrosis with marked elevation of serum amylase might have been a terminal event—the usual pain being masked by the comatose state Could there have been a neoplasm of the head of the pancreas? The early development of ascites in the absence of manifestations of sudden portal obstruction and the late development of jaundice make this seem unlikely Such reasoning applies to neoplasm primary in any other location

This patient was a metal burner The early development of ascites seems against a toxic etiology although one cannot rule it out on the evidence available

Primary carcinoma arising in a cirrhotic liver should be suspected when the course is unusually rapid It is relatively rare and there is positive evidence of acute pancreatitis another factor which would exert the same influence on the course of the disease

Most of the evidence is in favor of galloping cirrhosis with a terminal acute pancreatitis

Anatomical Diagnosis (Autopsy No 20535) Widespread acute necrosis of pancreas Nodular cirrhosis of liver with foci of acute necrosis Ascites Esophageal varices Jaundice Bile casts in renal tubules Dilatation of bile ducts and gallbladder Lobular pneumonia

The liver showed a nodular cirrhosis and also many small areas in which hepatic cells were freshly necrotic and surrounded by leukocytes The pancreas showed an unusual condition There were many areas of necrosis of the pancreatic tissue often bordered by an inflammatory reaction It was not at all the appearance of hemorrhagic pancreatitis in which rupture of blood vessels produces widespread hemorrhage and death of pancreatic tissue because of deprivation of blood supply The pancreatic ducts were not dilated The appearance was that of multiple infarcts and there were thrombi in the vessels Most appeared to be in veins but some were in arteries Under the microscope there were found to be areas of metaplasia of duct epithelium with partial occlusion of the ducts There were foci of greatly dilated acini It seemed probable that the pancreatic necroses were the result of this process with rupture of acinar tissue and escape of trypsin There were thrombosed vessels with segmented necrosis of the type caused by trypsin and one with a healed segmented necrosis indicating damage at an earlier date

SUMMARY This 40 year old metal worker had a rapidly progressive illness first with ascites then with attacks of vomiting followed by jaundice and death in coma five months after onset Examination revealed loss of weight ascites jaundice hepatomegaly, and splenomegaly Studies showed a leukocytosis obstructive jaundice with evidence of diffuse hepatic disease and a high serum amylase The ascitic fluid was bile stained transudate The various diseases in which ascites jaundice, and hepatomegaly might all be found were discussed The final diagnosis of rapidly advancing NODULAR CIRRHOSIS OF THE LIVER AND ACUTE PANCREATITIS was confirmed at autopsy

III

(#296495 Admitted October 10 1945 Died October 11 1945)

THIS 47 year old Negro woman was in a comatose state when she entered the hospital for the fourth time She died within a few hours without regaining consciousness

SUMMARY OF FIRST ADMISSION (July 13 to August 5 1943) The patient complained of abdominal swelling and dyspnea of two weeks duration Since January 1942 she had had frequent nosebleeds There had been a large intake of whiskey for several years Three weeks before entry she noted easy fatigability One week later dyspnea with ankle edema and abdominal swelling developed but there was no pain

Physical Examination T 100 2 P 118 R 38 B P 175/90 There was evidence of loss of weight and scattered brownish black macules were present There was edema of the legs and over the sacrum The mucous membranes were pale and icteric The retinal arteries showed moderate arteriosclerosis The cervical veins were moderately distended There were moist rales over both lung bases The heart was enlarged and a presystolic gallop was heard in the mitral area The aortic second sound was loud and a rough diastolic murmur was present transmitted downward to the left of the sternum The peripheral pulses were collapsing in type The abdomen was distended a fluid wave was present and there was shifting dullness A large firm mass filled the right side of the abdomen extending to the iliac crest The spleen was not enlarged Pelvic examination was normal

Course in the Hospital The temperature was normal She was digitalized and given potassium iodide. Paracentesis yielded one liter of clear transudate The jaundice persisted The mass did not change in size although the edema and ascites decreased After this the spleen was easily palpable

Laboratory Data Blood serologic test for syphilis positive titer 64 units hemoglobin 10 gm hematocrit 36 icterus index 25 sedimentation rate 41 mm per hour mean corpuscular volume 94 leukocyte count 6 000 with 60% polymorphonuclear cells and on several occasions an eosinophil count of 8% Stool examination normal Urine specific gravity 1 030 occasional red cell and white blood cell and a trace of albumin urobilin and bilirubin increased in urine phenolsulfonphthalein test 55% excretion in two hours hippuric acid excretion 0 total serum protein 8 gm % with albumin 2 7 Blood bilirubin total 4 3 mg % 2 9 direct alkaline phosphatase activity 22 7 units calcium 10 mg % and phosphorus 3 1 mg % Electrocardiogram showed normal sinus rhythm with left axis deviation

She was followed after discharge and the mass did not decrease appre

ciably in size She received 20 injections of bismuth during the following year and two doses of marpharsen following one of which she had a reaction

SUMMARY OF SECOND ADMISSION (May 4 to May 23 1944) The chief complaint was abdominal swelling Examination showed little alteration from the previous admission The lacrimal and parotid glands were thought to be enlarged She was pale and slightly icteric The abdominal mass was the same size The spleen was further enlarged and ascites was present There was a marked anemia with hemoglobin 5 3 gm and hematocrit 19 Other laboratory examinations included leukocyte count 5 400 with normal differential bilirubin 2 mg % with 1 4 direct serum protein 7 8 gm % with 4 8 gm % globulin phosphatase activity 17 5 units bromsulfalein test showed 25% retention in 30 minutes prothrombin activity was normal X ray of the chest showed marked enlargement of the heart particularly to the left with a dilated and tortuous aorta

SUMMARY OF THIRD ADMISSION (October 19 to November 11 1944) Nine days previously the patient had several teeth pulled and the gums bled profusely Three days before she had a chill followed by cough and pain in the right lower chest The day before she noticed jaundice Examination was unchanged except for signs of consolidation over the right lower lobe There was no ascites Bilirubin was 7 2 mg % with 5 3 direct The pneumonia gradually cleared She was given a transfusion On potassium iodide she developed nausea and vomiting and the drug was discontinued there having been no change in the size of the liver

SUMMARY OF FOURTH ADMISSION (October 10 1945) On September 25 1945 the patient was slightly icteric but stated that she felt well On October 10 she was brought to the hospital comatose and was found to have pulmonary edema The blood pressure fluctuated from 180/90 to 220/50 There was cervical rigidity and the pupils did not react to light The firm nodular abdominal mass extended well below the umbilicus The spleen was enlarged The tendon reflexes were hypoactive All limbs were flaccid except for the left leg which showed slight rigidity No clonus or Babinski sign was present The spinal fluid was grossly bloody with a red cell count of 1 1 million per cu mm Four hours after admission she became generally rigid and respirations ceased

DISCUSSION The central point of interest is the large mass which could be palpated on the right side of the abdomen The chronic icterus and the results of hepatic function tests leave little doubt that the mass was liver It had been present for over three years with little change in size Although the patient was persistently jaundiced ascites was less prominent on successive admissions Splenomegaly was present but no lymph node enlargement was noted

The most common cause of great enlargement of the liver is neoplastic disease but it would be distinctly unusual for the patient to survive for three years and for the mass to be present for such a long period without change in size The differential diagnosis if one

excludes such unlikely possibilities as cardiac cirrhosis liver abscess hydatid disease and tuberculoma of the liver seems to embrace five main possibilities

(1) Cirrhosis of the liver
(2) Lymphoma of the liver
(3) Sarcoidosis
(4) Subacute necrosis due to attacks of hepatitis possibly caused by a toxic agent with adenomatous nodules of regenerating liver tissue
(5) Syphilis of the liver—so called hepar lobatum

Occasionally in the course of Laennec s cirrhosis the liver is massive in size but rarely to the extent noted in this case Chronic jaundice of this degree and duration is uncommon and portal obstruction due to cirrhosis once evident rarely regresses while there is evidence of active liver disease *Hanot s cirrhosis is a rare disease which might* conceivably produce this picture but it seems unlikely

Hodgkin s disease may involve the liver predominantly on rare occasions and the splenomegaly is compatible with this diagnosis However after three years other lymphoid tissue should have been invaded and fever which was not present to any degree here except during the attack of pneumonia is usually a prominent feature of *abdominal Hodgkin s disease*

Chronic infectious hepatitis with necrosis of liver cells and adenomatous regeneration must be considered There were no acute attacks pointing to change in the activity of the process although the icterus did fluctuate in severity

Sarcoidosis is suggested by the parotid and lacrimal gland enlargement the increase in serum globulin and the history of cutaneous *lesions However no evidence of lymph node involvement* was ever noted and liver involvement of the degree observed here is rare in this disease

Syphilis of the liver with gumma formation rarely produces evidences of hepatic insufficiency However this patient had syphilis and the shape of the mass suggested a process which did not involve the liver uniformly These facts *combined with splenomegaly make this diagnosis possible* although there was little reduction in size of the mass with antisyphilitic treatment On the other hand the hepatic process ran a rather benign course and the ascites seemed to regress The persistent jaundice with high alkaline phosphatase level suggests biliary duct obstruction which might be explained by the scarring resulting from syphilis Portions of the liver might have been de-

stroyed and much of the palpable mass might have been adenomatous hypertrophy

Although this patient had arteriosclerosis and hypertension the aortic insufficiency was probably on a syphilitic basis in view of the marked peripheral signs Terminally there was sudden development of coma with the finding of a large amount of blood in the subarachnoid space The diagnosis of hemorrhage from a cerebral vessel seems inescapable When a large amount of blood gets into the ventricles following such an event spasticity is usually more evident than it was here The hemorrhage was probably from a basilar vessel in the region of the circle of Willis and may well have been from a congenital aneurysm or due to syphilis but degenerative arterial disease was the more probable cause

ANATOMICAL DIAGNOSIS (Autopsy No 19633) Generalized and intra renal arteriosclerosis Narrowing of the mouth of left coronary Scarring of myocardium Massive cerebral hemorrhage with subarachnoid extension Lobular pneumonia and chronic passive congestion of lungs History of positive serologic test for syphilis Syphilitic aortitis with involvement of aortic valve Aortic insufficiency Healed gumma and patchy scarring of the liver

The liver was reduced in size The surface showed distorted areas of scarring producing abnormal lobulation Small gray nodules projected through the capsule On gross section the structure was completely replaced by nodules of various sizes The spleen was enlarged Microscopically the aorta showed syphilitic aortitis The liver showed numerous rounded areas of hyalinized connective tissue which had the appearance of healed gummas There was also a rather widespread though patchy scarring with mononuclear cell infiltration

SUMMARY This 47 year old Negro woman had four admissions from 1943 to her death in 1945 There were hepatomegaly chronic mild icterus splenomegaly and signs of aortic insufficiency The jaundice persisted but ascites which was present at the onset gradually disappeared There was no progressive change in size of the liver She was anemic and had an obstructive type of jaundice with high serum alkaline phosphatase activity The blood serologic test for syphilis was positive but the liver size did not alter with antisyphilitic treatment Of the various causes of hepatomegaly considered SYPHILIS OF THE LIVER was chosen because of the benign course over several years with palpable evidence of irregular involvement of the hepatic substance chronic obstructive jaundice and the positive serologic test for syphilis Autopsy revealed healed gummas and patchy scarring of the liver

IV

(#13693 1st Admission November 11 to November 26 1901
2nd Admission December 30 1901 to February 2 1902)

THIS 64 year old white woman entered complaining of nervousness and stomach trouble with pain in the right side She had had nervous dyspepsia associated with nausea and regurgitation especially after meals There had been some loss of weight in the two years prior to admission

SUMMARY OF FIRST ADMISSION Thirteen weeks before admission she noted increase in her stomach trouble and pain in the right side She vomited often after eating and had taken nothing but whiskey and ice water for four weeks The pain was paroxysmal beginning in the right side posteriorly and running around to the front She noted frequency of urination and 10 weeks before entry had hematuria on one occasion She became weak and on several occasions passed blood clots per rectum She thought that she had had fever but denied chills

Physical Examination on admission T 98 2 P 96 R 24 The patient was a moderately well nourished woman who appeared pale Her legs were drawn up and it hurt to straighten them particularly the right one The lungs were normal The area of precordial dullness was small There was a soft systolic apical murmur The abdomen was large and pendulous and the flanks were full She held the abdomen tense making it impossible to examine her satisfactorily There was some resistance in the epigastrium and an indefinite mass was felt in the right lumbar region which was tender on pressure The pulse was collapsing in quality The following morning she was noted to be icteric

Course in the Hospital The next day Dr Thomas McCrae noted the *icterus and commented on loss of weight* There was resistance to palpation and pain on deep pressure under the right costal margin and the liver edge was barely palpable The following day Dr William Osler felt a hard firm mass on deep palpation in the right upper quadrant which descended on inspiration Dr William S Halsted felt a round sharp liver edge at the costal margin The patient gradually improved and her icterus was thought to lessen Resistance to palpation in the right flank continued and the liver edge could be felt 2 cm below the costal margin at the time of discharge

Laboratory Data Examinations showed urine normal hemoglobin 70% leukocyte count 10 000 She had no fever

After discharge she grew rapidly worse She vomited several times daily The pain in her right side persisted was increased by any movement and radiated into the right iliac region

SUMMARY OF SECOND ADMISSION Examination showed the patient to be very pale with a wasted appearance There was tenderness on palpation in the epigastrium and on the right side with resistance to pressure The liver edge was 7 cm below the costal margin and 7 cm above the umbilicus in the median line There were tenderness over the 8th 9th and 10th right interspaces in the anterior axillary line and acute pain on pressure in the angle between the 12th right rib and the vertebral column The upper border of liver dullness was at the 6th rib in the right median line The spleen was not palpable On deep palpation in the left hypochondrium some observers felt an indefinite nodular mass There was marked varicosity of the veins of the legs

Course in the Hospital On January 3 Dr Osler felt the edge of the liver 3 fingerbreadths below the costal margin It was hard and in the nipple line a distinct irregularity was described Rectal and pelvic examinations revealed no abnormalities The liver continued to increase in size but the jaundice did not deepen The patient s weight declined from 137 to 121 pounds during observation and on occasions the temperature rose as high as 102 but was usually between 99 and 100

Laboratory Data Hemoglobin was 61% leukocyte count 8 800 with 15% mononuclears 3% transitional cells and 82% polymorphonuclears Urine showed a trace of albumin few leukocytes and hyaline casts and a trace of bile

DISCUSSION This case selected from the files of the early days of this hospital was observed by Dr Osler Fifty years ago only very simple laboratory procedures were available so that sound conclusions had to be reached primarily on the basis of careful evaluation of the clinical facts alone It is particularly appropriate to use this setting for one of these conferences in view of the growing tendency in medical center practice to believe that an accurate diagnosis cannot be made without prior accumulation and interpretation of laboratory reports

In this case the facts were collected many years ago Our problem is to place ourselves in the position of Dr Osler and his colleagues and to see what conclusions can be reached by an analysis of these facts There was progressive increase in the size of the liver and the presence of a separate mass deep on palpation which moved with the liver Let us consider the possible causes of the hepatomegaly under three major headings (1) Neoplasm either primary or secondary Of the secondary tumors involving the liver one would have to consider Hodgkin s disease carcinoma of the body or tail of the pancreas carcinoma of the colon or stomach, and neoplasm of the kidney (2) Certain metabolic diseases which may be responsible for progressive and diffuse hepatic enlargement such as amyloidosis and

cirrhosis of the liver (3) Some type of infection—a peculiar hepatitis tuberculosis sarcoidosis or a localized abscess or abscesses following one of three events a ruptured diverticulum a ruptured retrocecal appendix or an amebic infection of the liver

As we review the various manifestations that were exhibited during the course of this disease it would seem reasonable to assume that the patient did not have diffuse hepatocellular involvement and that there was no obstruction of the common bile duct as the jaundice was neither progressive nor intermittent There was no splenomegaly no hemorrhagic tendency and no evidence of portal obstruction The disease was characterized primarily by pain and tenderness and was of many weeks duration before there was evident enlargement of the liver

There was no apparent basis for the development of secondary amyloidosis and no involvement of other organs to suggest either the primary or secondary form of this disease There were none of the stigmas characteristic of Laennec s cirrhosis of the liver The degree of pain and tenderness would be against this possibility

It would seem altogether unlikely that the patient had a primary neoplasm of the liver These are frequently associated with cirrhosis but rarely with the type of pain exhibited by this patient Carcinoma originating in the gallbladder may be accompanied by severe pain but an irregular hepatic enlargement usually comes early in these cases Hodgkin s disease confining itself to the liver in a patient of this age without evident lymph node involvement elsewhere would be unusual She might have had a secondary neoplasm of the liver The association of what may have been thrombophlebitis suggests the possibility of carcinoma of the pancreas The location of the pain the constipation and the history of bleeding per rectum might indicate a carcinoma of the colon Gastrointestinal symptoms had been present for years so that this aspect is difficult to evaluate Carcinoma of the stomach is certainly not common in females of this age A tumor of the kidney with metastases to the liver should be considered The bout of hematuria might thus be explained Obviously the progressive enlargement of the liver makes neoplasm a strong possibility However she apparently had pain from the very outset The persistence of the pain the fever both early and late in the course of the illness and the predominance of polymorphonuclear cells in the differential count point to some peculiar type of infection The duration of the illness and the absence of progressive jaundice make

it unlikely that she had diffuse hepatitis of any sort The pain and the lack of any evidence of tuberculosis or sarcoidosis elsewhere, would seem to rule out these diagnoses

It is quite possible that there was a localized abscess or abscesses in the liver As one looks over the possibilities, three sources for abscess formation come to mind (1) a ruptured colonic diverticulum with secondary infection of the liver (2) a perforated retrocecal appendix with pylephlebitis, and (3) an amebic infection of the liver with abscess formation The long duration of the illness suggests an *unusual type of infection and renders very unlikely the possibility* that it arose from a perforation of the appendix or large bowel Certainly in the days before antibiotics a patient would not have survived pylephlebitis for six months On the other hand all of these points which have been raised against the diagnosis of a pyogenic infection seem to favor a diagnosis of amebic abscess The choice seems to lie between this diagnosis and that of metastatic carcinoma of the liver I shall choose the diagnosis of amebic abscess for reasons given above Here again we have had a choice between a diagnosis which carries a hopeless prognosis and one which offers a prospect of successful therapy We have followed the principle of selecting the latter when the facts allow it

Now that a diagnosis has been made the final step is to review the important evidence, both positive and negative to see whether it adequately explains all of the findings An amebic abscess is a chronic lesion which may persist in varying degrees of activity for many years Such an abscess projecting near the surface of the liver could cause the persistent pain and spasm No longer puzzling would be the blood clots passed by rectum early in the illness The digestive symptoms the loss of weight and intermittent fever are logical consequences of this disease The progressive enlargement of the liver the absence of progressive jaundice the anemia, and the absence of splenomegaly are all adequately explained Difficult to account for is the history of hematuria

ANATOMICAL DIAGNOSIS (Autopsy No 1863) Hepatic abscess amebic, with adhesions to surrounding tissues invasion of the right kidney Arteriosclerosis Bronchopneumonia emphysema of the lungs

There was a very large abscess in the liver which was filled with grumous material in which amebas were found and from which staphylococci were cultured Extension of the infection to the region of the right kidney had obviously been present for some time and provided an explanation for the peculiar location of the pain and the history of hematuria early in the course of the illness

SUMMARY This 64-year old white woman who had had stomach trouble for many years developed pain in the right side with nausea and vomiting three months before admission She had hematuria on one occasion and passed blood clots per rectum several times There were progressive loss of weight chronic icterus persistent tenderness and spasm in the right upper quadrant and the gradual development of a large mass in this area She had a mild anemia but no definite leukocytosis and only an occasional mild febrile reaction The various causes of hepatomegaly were considered and two possibilities were discussed in detail carcinoma and abscess The pain and the persistent tenderness and spasm made abscess more likely and of the various types of abscess the one most likely to be associated with a progressively enlarging right upper quadrant mass was considered to be an AMEBIC ABSCESS OF THE LIVER This proved to be the correct diagnosis

V

(#370221 Admitted December 4, 1945 Died December 9, 1945)

THIS 60 year old Negro man complained of abdominal swelling of five weeks duration For four years his diet had been deficient There was no history of alcoholism

Three years before he developed varicosities followed by ulceration of both legs Five months before he noticed swelling of the ankles This persisted and five weeks before entry progressed to involve the legs the thighs and the abdomen He noticed dyspnea but had no orthopnea There was a feeling of fullness after meals but no pain

PHYSICAL EXAMINATION on admission T 99 P 88 R 20 BP 160/90

The mucous membranes were pale There was no icterus The retinal vessels were narrowed There was no engorgement of the cervical veins and no lymph node enlargement The lungs were clear After removal of ascitic fluid the cardiac impulse was felt in the 6th interspace in the anterior axillary line and the left border of the heart was 13 cm to the left in *the 6th interspace There was a blowing systolic murmur in the mitral area* and in the aortic region where the second sound was ringing in character The radial arteries were thickened There was marked ascites Rectal examination was normal There was swelling of both legs more marked on the left with pitting up to the abdomen

COURSE IN THE HOSPITAL After removal of 9 liters of straw colored peritoneal fluid a firm nodular liver edge was felt 3 fingerbreadths below the costal margin Vomiting and diarrhea developed and he became disoriented and incontinent The temperature rose to 102 The abdomen remained soft but there was tenderness in the upper quadrants The blood pressure fell to a lower level the extremities became cold and the peritoneal fluid reaccumulated rapidly The patient became comatose and unresponsive

LABORATORY DATA Hemoglobin 13 gm leukocyte count 5 100 with normal differential count The urine had a specific gravity of 1 030 5 to 10 white blood cells and an occasional red blood cell per high power field, urobilinogen *positive 1 64 dilution Blood serologic test for syphilis* negative icterus index 60 serum bilirubin 3 7 mg % with direct reacting 2 1 total serum protein 6 2 gm / with 2 3 gm % albumin bromsulfalein excretion test 36/ retention in 30 minutes cephalin flocculation 4 plus the stool showed a positive guaiac reaction Examination of ascitic fluid 1st tap showed specific gravity 1 010 leukocytes 100 per cu mm all mononuclear cells Culture sterile On the 2nd tap the fluid was cloudy

specific gravity 1 011 leukocytes 14 000 7% mononuclears and 93% polymorphonuclear cells Cultures of both ascitic fluid and blood at this time showed heavy growth of *Escherichia coli*

X ray of the chest showed an increase in transverse diameter of the heart particularly the left ventricle Aorta was slightly dilated with small deposit of calcium in arch Lungs showed bilateral congestive changes with linear shadows most likely due to atelectasis

DISCUSSION Ascites and hepatomegaly were the major clinical findings in this case The ascitic fluid when first examined had the characteristics of a transudate and was sterile The final paracentesis revealed material of a different character with increase in the white cells most of which were polymorphonuclear cells and *E coli* was grown It seems evident that this peritonitis and bacteremia was a terminal event and not the basic cause of the ascites There was no clinical evidence of a primary peritonitis when the patient was first examined

Thrombosis of the portal vein is most frequently associated with portal cirrhosis or intra abdominal malignant disease The clinical picture is determined by the site and extent of the thrombosis and the rate at which the vein is occluded Rapid occlusion usually results in hematemesis acute development of ascites and death whereas in slow closure there is time for collateral circulation to develop and the manifestations are those of splenic anemia with splenomegaly leukopenia and periodic gastrointestinal hemorrhages none of which was present in this case Obstruction of the portal vein by extrinsic masses such as a neoplasm or one of many other diseases resulting in lymph node enlargement may occur but with the evidence of intrinsic liver disease which was present here these would not completely explain the picture

In view of the cardiac enlargement the murmur and the edema of the legs the question arises whether the patient had ascites and hepatomegaly as a result of heart failure Generally hepatomegaly in cardiac failure goes hand in hand with engorgement of the veins which was not present in this patient The dyspnea was not accompanied by orthopnea and was probably the result of elevation of the diaphragm due to the ascites In addition to the enlargement of the heart there was arteriosclerosis of the peripheral vessels and the aorta so it is probable that this patient had arteriosclerotic cardiac disease but in the absence of chronic failure this would not account for the ascites and hepatomegaly It seems more likely that the hard nodular liver with evidence of marked impairment of function was the seat of intrinsic disease One therefore has left for consideration

those diseases of the liver which result in hepatomegaly and portal obstruction

Syphilis of the liver is rare and it usually does not cause ascites, although this complication may result from scarring or pressure of a gumma in the porta hepatis Diffuse sarcoidosis of the liver is also infrequent and in this case there was no lymph node enlargement or other characteristic lesions In the various types of lymphoma the spleen is usually enlarged and here there was no involvement of the superficial lymph nodes Hodgkin s disease of the liver is not usually sufficiently extensive to produce portal obstruction of this degree Metastatic neoplasms must be mentioned but here again portal obstruction is unusual and there was no evidence to suggest a primary source of a neoplastic growth.

Cirrhosis of the liver seems to be the best explanation of the hepatic disease Portal obstruction is quite common and jaundice of this degree is not unusual Peripheral edema appears to be related in many instances to lowering of the serum albumin level, which was noted in this case The liver was not greatly enlarged and felt diffusely nodular Primary carcinoma not infrequently develops in a cirrhotic liver but there is no definite basis on which its presence could be postulated in this patient except possibly the rather rapidly fatal course This however has a more likely explanation in the terminal bacteremia The occurrence of both ascites and jaundice carries a bad prognosis in cirrhosis of the liver, and approximately 50% of the patients are dead within six months of their appearance Intercurrent infections are an important cause of death in this disease and peritonitis and bacteremia are not uncommon

ANATOMICAL DIAGNOSIS (Autopsy No 19716) Healed widespread liver necrosis Primary liver cell carcinoma with metastasis in lungs Esophageal varices Congestion and fibrosis in spleen Ascites and edema of lower extremities History of paracentesis Subacute and organizing peritonitis and acute inflammation around pancreas and kidney pelves Focal myocardial scarring Arteriosclerotic plaques in coronary arteries Arteriosclerosis of intrarenal arteries slight

The lungs aside from some edema showed several white nodules in the anterior portion The liver was large The surface was nodular and on section the nodules varied from 1 mm to 4 cm in diameter Some were pink some gray and some distinctly bile stained The spleen was enlarged The liver had clearly been the site of a widespread and massive necrosis which had healed leaving broad scars These often occupied almost an entire low power field The scarring was more extensive than occurs in ordinary nodular cirrhosis that is the bands of scar tissue and areas replaced were much wider There were nodules of regenerated liver tissue

and arising individually in many of these were nodules of carcinoma that varied in size from small groups of cells to large masses Some formed acini with wide lumina There were metastases in the lung This seemed to be an instance of carcinoma of the liver of multiple origin suggesting that there may have been an abnormal conversion of a bile acid or cholesterol into a carcinogenic agent

SUMMARY This 60 year old Negro man five months before death developed ankle edema which progressed to involve the legs and abdomen Examination revealed pallor cardiac enlargement a systolic murmur peripheral arteriosclerosis edema and ascites After removal of 9 liters of ascitic fluid a nodular liver became palpable There was slight elevation of serum bilirubin and various tests showed impairment of hepatic function He developed an acute peritonitis with *Escherichia coli* bacteremia In the absence of venous hypertension the likely cause of the ascites was hepatic disease with portal obstruction Consideration of the possible hepatic diseases present led to a diagnosis of cirrhosis with possible PRIMARY CARCINOMA OF THE LIVER superimposed At autopsy there was wide spread healing LIVER NECROSIS with very broad scars unlike ordinary Laennec s cirrhosis There were nodules of regenerating liver tissue and arising individually in many of these areas were nodules of carcinomatous tissue



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sequence of events is frequently observed in Hodgkin s disease Tuberculosis usually produces localized enlargement of lymph nodes but occasionally one sees symmetrical and essentially uniform generalized lymphadenopathy This may occur in the absence of pulmonary tuberculosis and the resulting picture may closely simulate that of a primary lymphatic disease, such as Hodgkin s disease or leukemia It may be added that extensive tuberculosis of the lymph nodes may complicate other diseases such as systemic lupus erythematosus or Hodgkin s disease

Table 13 Causes of Lymph Node Enlargement

I Generalized lymph node enlargement
- A Infections
  - 1 Acute (common communicable diseases infectious mononucleosis plague generalized dermatitis or furunculosis)
  - 2 Chronic (syphilis tuberculosis sarcoidosis)
- B Hypersensitivity reactions and collagen vascular disease
  - 1 Serum sickness
  - 2 Systemic lupus erythematosus
  - 3 Rheumatoid arthritis and Still s disease
  - 4 Hypersensitivity to drugs and other agents
- C Primary lymphatic disease
  - 1 Hodgkin s disease
  - 2 Lymphosarcoma
  - 3 Reticulum cell sarcoma
- D Leukemia

II Localized lymph node enlargement
- A Infections
  - 1 Syphilis
  - 2 Tularemia
  - 3 Lymphopathia venereum
  - 4 Granuloma inguinale
  - 5 Tuberculosis
  - 6 Acute bacterial infection (staphylococcal streptococcal)
  - 7 Fungus or parasites
  - 8 Cat scratch disease
- B Metastases from a malignant tumor
  - 1 Axillary in breast carcinoma
  - 2 Cervical in nasopharyngeal carcinoma
  - 3 Supraclavicular from lung or gastrointestinal neoplasm
- C. Congenital abnormalities
- D Diseases causing generalized enlargement may present with local enlargements such as axillary or cervical glands in Hodgkin s disease

The nodes which are along the line of lymphatic drainage of an area of acute inflammation may attract greater attention than the

primary site of infection For example large inguinal buboes due to the gonococcus may be found in the absence of obvious urethritis Similarly in the ulcero glandular form of tularemia and in the localized lymphadenopathy of cat scratch disease the lesion at the portal of entry may be so insignificant as to escape notice Scrofula a form of tuberculous adenitis which was common prior to the routine adoption of pasteurization of milk frequently had its origin in an unrecognized tuberculous focus in one of the tonsils As with infections so also with metastatic neoplastic disease the location of the affected nodes may in itself lead to disclosure of the site of the primary growth A hard node concealed behind the left clavicle (Virchow node) may be the only physical sign of a carcinoma of the stomach Nodes in this same region may also harbor metastases from an unsuspected pulmonary carcinoma Metastatic involvement of the cervical nodes may be due to a small nasopharyngeal carcinoma which has caused trivial local symptoms and which may be detected only by nasopharyngoscopic examination

The physical characteristics of enlarged lymph nodes may have as great diagnostic significance as their location When the enlargement is due to an acute inflammation of the node the overlying skin may be warm and red and the node may be exquisitely tender The nodes of sarcoidosis and of chronic leukemia are firm rubbery and nontender whereas those of acute leukemia tend to be softer and may be moderately tender With tuberculous adenitis the nodes are usually firm and have a tendency to adhere to one another and to the skin and other neighboring structures They may become fluctuant and eventually discharge their necrotic contents In Hodgkin s disease the nodes even when greatly enlarged remain as discrete rubbery masses without attachment to other tissues Lymph node containing metastatic carcinoma have a degree of hardness which with slight exaggeration may be described as *stony* A similar stony hardness may be noted in old tuberculous nodes which have become fibrosed and calcified A roentgenogram of the involved area will reveal the calcium deposits

The cause of the lymphadenopathy is occasionally disclosed by the associated findings a leukemic blood picture the characteristic lesions of sarcoid in the small bones of the hands the discovery of L E cells positive bacteriological cultures or immunological tests However in many instances the final diagnosis depends upon lymph node biopsy This should not be too long deferred if the diagnosis is in doubt When nodes are selected for biopsy it is best to select a

large one, and preferably more than one should be examined In guinal nodes and nodes which have been irradiated should be avoided if possible All portions of the excised tissue should be examined since the significant lesions may be confined to a relatively small area while the remainder of the node may show only hyperplasia

Splenomegaly

The spleen has long been considered a rather mysterious organ It has a complex structure and there is no doubt that it performs a variety of functions yet its presence is not essential to the maintenance of health It is involved in a number of diseases and when involved it may become enlarged to a variable degree However in some of the diseases in which the spleen appears to play an important role there may be no detectable splenomegaly This is true of the syn dromes characterized by hematopenia (thrombocytopenia neutro penia hemolytic anemia, panhematopenia) Absence of clinically de tectable splenomegaly is the rule in idiopathic thrombocytopenic purpura

The history the physical examination and the routine laboratory studies will serve to establish the diagnosis in many cases in which the prominent feature is splenomegaly but in the more complicated problems other tests may be of value such as blood cultures sero logical procedures sternal marrow examination tests of hepatic func tion and roentgenological studies As in all other situations search for and proper interpretation of any associated findings are of vital importance The coexistence of lymphadenopathy hepatomegaly jaundice or ascites will serve to narrow down the possibilities The diagnosis of a number of diseases which may be associated with splenomegaly such as leukemia pernicious anemia congenital hemo lytic icterus and others can be readily made by appropriate studies of the peripheral blood

In palpating the abdomen to determine the size of the spleen good relaxation is essential This may often be obtained by having the patient place his left hand under the left flank thus raising this side of the body a little from the bed Gentle palpation mus be carried out, or the edge of a soft spleen such as that seen in typhoid fever may be missed If the spleen is very large its edge may extend well

down in the left lower quadrant or be below the iliac crest There fore palpation should begin with the hand low over the abdomen and working upward toward the left flank as the examination proceeds *Palpation of the splenic notch is helpful in identification* Auscultation should always be carried out to detect a bruit or friction rub Numerous other masses appearing on the left side of the abdomen may be difficult to differentiate from spleen A large kidney may

Table 14 Causes of Splenomegaly

I Infections
- A Acute infections with acute splenic tumor (typhoid fever tularemia, typhus communicable diseases etc)
- B Subacute and chronic infections (bacterial endocarditis tuberculosis syphilis histoplasmosis brucellosis etc)
- C Parasitic diseases (malaria kala azar hydatid disease etc)

II Congestive splenomegaly
- A Portal hypertension
  1 Cirrhosis of the liver
  2 Banti s syndrome
- B Thrombosis of splenic or portal veins
- C External pressure on splenic or portal veins by glands tumors etc

III Blood dyscrasias
- A Anemias (due to bone marrow replacement pernicious anemia hemolytic anemias etc)
- B Polycythemia
- C Leukemia
- D Primary splenic neutropenia and panhematopenia (hypersplenism)

IV Due to presence of abnormal tissue hemorrhage collagen vascular disease
- A Granulomatous diseases (Hodgkin s disease lymphosarcoma sarcoidosis reticulum cell sarcoma etc)
- B Malignant tumors
- C Lipodystrophies (Gaucher s disease etc)
- D Benign tumors and cysts
- E Amyloidosis
- F Subcapsular hemorrhage (injury infectious mononucleosis)
- G Serum sickness
- H Systemic lupus erythematosus

descend with respiration but is situated more deeply and does not usually have a firm edge In doubtful cases pyelograms should be made Other conditions to be distinguished are pancreatic cyst tumor of the splenic flexure or stomach ovarian cyst omental mass with tuberculous peritonitis mesenteric cyst retroperitoneal tumor and neoplasm of the adrenal

Once the mass has been definitely identified as spleen then its relative size is an important aid in diagnosis Massive enlargement of the spleen is most common in leukemias of the chronic type The

organ may reach large size in chronic malaria and occasionally in certain types of lymphoma In the younger age group it may be quite large in cases of congestive splenomegaly with portal hypertension Rarely hemorrhage beneath the capsule will produce a massive tumor this may occur in infectious mononucleosis or after trauma In some of the lipoidoses such as Gaucher s disease the very large spleen may be a source of discomfort to the patient

When the spleen is only moderately enlarged then the problem in diagnosis is greater At some stage in all of the diseases mentioned above the organ is not very large and in numerous other diseases it never exceeds moderate size In the latter class fall the various infections associated with acute splenic tumor The lymphomas may simulate an infection and there may be only moderate enlargement of the spleen without any increase in size of the superficial lymph nodes A practical point to remember is the enlargement which may take place in the spleen when it is the seat of extramedullary blood formation as in cases of progressive myelofibrosis

During recent years a great deal of attention has been devoted to the relationship of the spleen to the bone marrow and the various clinical syndromes designated as hypersplenism In certain of these syndromes although the hematologic abnormality may be restored to normal by removal of the spleen that organ is not the seat of any recognizable disease This is the situation in so called primary hypersplenism Similar changes in the hematological picture may follow involvement of the spleen in a variety of acquired diseases—so-called secondary hypersplenism These conditions have been divided by Von Haam and Awny into six groups

(1) Congestive splenomegaly including Banti s syndrome and acquired hemolytic icterus
(2) Infiltrative splenomegaly as illustrated by the xanthomatoses
(3) In chronic leukemia there may develop an acute hemoblastic splenomegaly without evidence of exacerbation of the disease in other respects
(4) Splenomegaly secondary to chronic infection such as tuberculosis and syphilis
(5) The rare instances of neoplastic involvement of the spleen
(6) Splenomegaly secondary to progressive myelofibrosis

The lymph nodes and the spleen as has been pointed out are involved in many diseases Their enlargement may constitute the only objective findings which can serve as a basis for analyzing the diagnostic possibilities

Illustrative Cases

I

(#308110 Admitted Jan 3 1946
Biopsy of lymph node Jan 21 1946)

THIS 62 year old farmer was admitted because of fever and enlargement of lymph nodes He had been studied in 1943 because of severe epistaxis Examination revealed benign prostatic hypertrophy The blood serologic test for syphilis was negative hemoglobin was 10 gm leukocyte count 9 900 with 73% polymorphonuclear cells bleeding and clotting time were normal urinary sediment showed an occasional white blood cell

In December 1945 five days after extraction of three teeth he developed cramps in the leg muscles They spread to his shoulders arms and other muscular groups and were progressive in severity Two weeks later he noticed a swelling in the cervical region which fluctuated rapidly in size and was tender An eruption appeared on his back and shoulders and spread to his arms legs and feet These lesions were tender to touch He noticed fever and anorexia There was generalized weakness and the muscular cramps continued For several months he had had a gnawing pain in the epigastrium with eructation of gas and regurgitation Food eliminated this discomfort as did aluminum hydroxide

PHYSICAL EXAMINATION on admission T 101 8 P 112 B P 120/70

There was no jaundice pallor or edema There was an erythematous papular eruption most marked over the back and arms The lesions were confluent over the back but discrete over the extremities It burned but did not itch There was generalized enlargement of the lymph nodes including the cervical axillary and inguinal areas The lungs were normal The heart sounds were distant the rhythm was regular The peripheral arteries were thickened The liver was palpated 3 cm below the costal margin The spleen was not enlarged The joints were all tender to touch as were the muscles The reflexes were sluggish

COURSE IN THE HOSPITAL On the fifth hospital day the rash was disappearing The temperature which was elevated during the first four days gradually fell to normal

LABORATORY DATA Hemoglobin was 13 9 gm hematocrit 40 icterus index 5 leukocyte count 5 000 to 7 150 with 10% juvenile neutro-

phils 44% segmented neutrophils 25% eosinophils 11% lymphocytes and 6% monocytes A second differential showed 31% eosinophils Skin test with trichina antigen was negative Gastrointestinal series showed no organic lesion in the esophagus stomach or duodenum

SUBSEQUENT COURSE The patient was discharged on January 11 and readmitted on January 18 The rash had disappeared but the fever promptly returned The day before admission his temperature was 104 Re-examination showed no eruption edema cyanosis or jaundice All the superficial lymph nodes were enlarged firm and tender The liver was palpated Further notes described a complete cervical collar of nodes up to 2 cm in diameter The axillary nodes were huge A splenic edge was felt 2 cm below the costal margin The temperature gradually fell He was sent for lymph node biopsy On this admission leukocyte count was 3680 with 34 segmented neutrophils 23% juvenile neutrophils 2% eosinophils 26, lymphocytes and 6% monocytes Platelets were 160 000 and blood culture showed no growth He died a few days after the biopsy was taken

DISCUSSION The outstanding features were fever a *transitory* skin eruption generalized lymph node enlargement hepatomegaly and splenomegaly The differential diagnosis revolves about a large group of diseases in which all of these manifestations might be present Certain diseases such as syphilis tuberculosis and sarcoidosis seem unlikely The blood serologic test for syphilis was negative and no mucous membrane lesions were present to suggest secondary syphilis *Tuberculosis* with symmetrical enlargement of the lymphatic structures may occur but is exceedingly rare at this age There was no evidence of pulmonary tuberculosis The rapidity of onset of this illness the type of eruption and the massive size of the glands would be against sarcoidosis

Infectious mononucleosis is unusual in elderly individuals There was no evidence of oropharyngeal involvement which is so prominent a manifestation in this illness The exanthem usually resembles that of measles or of another of the acute infectious diseases No abnormal lymphocytes were seen in the smears We know that this disease ended fatally which almost never occurs in uncomplicated mononucleosis although rupture of the spleen has been reported At this patient s age one must consider *metastatic* neoplastic disease but no primary tumor was discovered Generalized adenopathy of this degree would be most unusual although it has been described with carcinoma of the lung and of the stomach

There are left the following possibilities which need more detailed consideration (1) acute lymphatic leukemia (2) lymphoma of either

the Hodgkin s lymphosarcoma or reticulum cell sarcoma type (3) acute dermatomyositis (4) acute lupus erythematosus

Acute leukemia is a rapidly fatal disease which frequently starts with symptoms suggesting infection development of a leukoblastic blood picture and a hemorrhagic tendency There may be extreme prostration weakness high fever varying degrees of lymphadenop athy hepatomegaly and splenomegaly and gastrointestinal disturb ances such as anorexia vomiting and diarrhea Tenderness over the bones may be associated with symptoms suggesting acute arthritis Leukemic infiltration of the skin occurs but would hardly regress in as short a period of time as did this eruption With such rapid devel opment of node enlargement, more definite changes would have been expected in the peripheral blood although this does not occur invariably

Hodgkin s disease usually begins with localized swelling of one group of nodes ordinarily those in the neck before the others en large There is often enlargement of the spleen and in the course of weeks or months generalized adenopathy may occur—especially marked in the axillary and mediastinal regions There is rarely an acute onset with almost simultaneous enlargement of all of the super ficial nodes Skin eruptions of the so called id type which are non specific and not associated with actual cutaneous infiltration may occur They are maculo papular or urticarial in type or may even be bullous or vesicular Early in the disease there may be a lympho cytosis and often eosinophilia particularly when there is necrosis in the lymph nodes Under such circumstances the nodes may be tender as they were in this case There may be little or no clinical distinction between lymphosarcoma and Hodgkin s disease *Lymphosarcoma* is especially likely to affect the mediastinal glands and splenomegaly is the exception rather than the rule Some cases terminate fatally within a few months Spontaneous periods of quiescence may occur during which a large group of nodes may disappear almost com pletely This patient s nodes supposedly fluctuated in size at the be ginning of the illness In general the nodes form larger mas es than in the Hodgkin type of lymphoma Large lymphocytes may be seen in the peripheral blood suggesting the possibility of a true lympho sarcoma cell leukemia Such a state may be precipitated by x ray therapy with the development of a fulminating disease pict ure In view of the tendency of lymphosarcoma to invade the tissu es it is not surprising that some cells enter the blood stream This may have

happened in the present case In cases of *reticulum cell sarcoma* the most common manifestation is enlargement of the superficial lymph nodes It should always be suspected when the nodes are painful Also an acute fulminating course is more frequent than in the other types of lymphoma About 20 per cent of the patients have involvement of the gastrointestinal tract, which might account for the symptoms described in this case However the liver and spleen are not so commonly enlarged and cutaneous manifestations are almost unknown

Follicular lymphoblastoma may be confused in the early stages with chronic non specific inflammatory conditions involving the lymph nodes but it is well to remember that chronic lymphadenopathy in the adult is rarely due to non specific inflammation alone *Follicular* lymphoblastoma is usually considered to be benign but it may progress to a malignant stage It is considered by some to be a form of lymphosarcoma It is most common in middle aged and elderly individuals and slightly more prevalent in men The onset is usually insidious and systemic symptoms are not common as in other types of lymphoma Anemia does not develop and the leukocytic picture is normal Involvement of the spleen is uncommon

The last two diseases to be considered are systemic in nature may closely resemble each other have protean manifestations and may develop suddenly and run a fulminating course *Acute dermatomyositis* may be seen in older individuals with a predilection for males Muscular pains are common and cutaneous lesions occur which in the early stage might be compatible with what this patient had Lymphadenopathy is not as common and rarely is as pronounced as in the other diseases discussed Eosinophilia may be present and the disease at onset may closely simulate trichinosis In *acute systemic lupus erythematosus* the skin lesions may be erythematous and multiform in character as here and may appear intermittently Fever likewise may be intermittent There are numerous instances on record in which the disease was precipitated in a fulminating form by minor procedures such as dental extraction or biopsy Gastrointestinal symptoms which may simulate gallbladder disease or peptic ulcer occur frequently The liver and spleen may be enlarged Lymphadenopathy is usually not as prominent as in this case but appears most often in those cases developing after minor operative procedures The nodes are usually tender Pains about joints are more common than are muscular aches

One must take into account the possibility that the eruption was due to some drug which the patient had been receiving and that the eosinophilia was due to the skin eruption and not to any underlying disease From the description the exanthem seems to fit the picture of erythema multiforme Eosinophilia of this degree would be un usual There was no history relating the onset of the eruption to a specific drug

The nature of the eruption the tenderness of the nodes the mus cular aches and joint tenderness the acute onset and the severity of symptoms tempt one to postulate that the patient had one of the diffuse arterial diseases such as systemic lupus erythematosus How ever the massive size of the nodes and the intermittency of the fever are in favor of some type of lymphoma Furthermore fulminating lupus erythematosus would be unusual in a male of this age

ANATOMICAL DIAGNOSIS (Autopsy No 19793) Lymphosarcoma Generalized lymph node involvement Tumor in portal areas of liver and partially replacing Malpighian bodies of spleen Great splenomegaly with large areas of necrosis Benign rectal polyp Cystitis cystica Slight chronic pyelitis Chronic inflammation in esophagus Purulent bronchitis

The hilar and peritracheal nodes were large and pigmented The liver was large and soft and the lobulations were distinct At one side of the common bile duct there were two large lymph nodes measuring 4 cm in diameter These may have pressed on the common duct causing partial occlusion of its lumen The lymph nodes were soft and on section showed a mottled brownish yellow color The spleen was large and firm and in its mid portion there was a pearly yellow plaque Extending beneath this to a distance of 4 cm was a large necrotic area Along the cardia of the stomach near the lesser curvature there were two large lymph nodes There were also small clusters of nodes found about the lower aorta Microscopic sections showed this to be a lymphosarcoma but the type was difficult to determine There was considerable pleomorphism but numerous cells with indented nuclei suggested that the tumor was a mono cytoma In addition there was everywhere phagocytosis of necrotic debris in the cells In the spleen the normal architecture was still distinct and the tumor seemed confined to the Malpighian bodies The large necroses were in tumor nodules The liver was peppered with tumor always originating in portal spaces and extending into the lobules

SUMMARY This 62 year old farmer developed severe muscle cramps five days after dental extractions and two weeks later noted tender swollen cervical lymph nodes which fluctuated in size A generalized tender cutaneous eruption appeared and he developed anorexia and fever with generalized weakness irrationality and a gnawing epigastric pain The outstanding features on examination were fever a transitory erythematous papular eruption generalized lymphadenopathy hepatomegaly and

splenomegaly The leukocyte count was normal or low and the differential count on one occasion revealed a 25% eosinophilia The nature of the eruption the tenderness of the nodes the muscle aches, the fever and the acuteness of onset suggested acute lupus erythematosus However the massive size of the nodes the intermittency of the fever and the definite hepato splenomegaly were more in favor of a lymphoma Autopsy revealed LYMPHOSARCOMA with generalized lymph node enlargement, tumor in the portal area of the liver and splenomegaly with large areas of necrosis

II

(#260029 First admission May 11 1942 to July 9 1942
Second admission October 10 1942 Died November 8 1942)

THIS 46 year old Negro woman entered because of a draining mass in the right axilla In 1932 she had had a polyarthritis In October 1932 she developed secondary syphilis Irregular antisyphilitic therapy was instituted In 1937 after skinning a rabbit she developed a local ulcer on the hand with nodal enlargement along the arm and formation of a sinus in the right axilla The illness which lasted three months was accompanied by cough dyspnea prostration and fever

In April 1942 she noticed a tender swelling in the right axilla which grew to 6 cm in diameter Chilly sensations and a temperature of 103 followed Local compresses were begun and sulfathiazole given but the lesion grew worse The leukocyte count was 26 000 She was admitted with a diagnosis of recurrent tularemia

SUMMARY OF FIRST ADMISSION The patient had a temperature of 102° There was enlargement of the cervical nodes on the right An extremely large tender matted firm partially fixed mass of lymph nodes was palpated in the right axilla The lungs were clear A systolic murmur was heard in the mitral area The left pupil was irregular and reacted poorly to light The knee and ankle jerks were absent

The urine contained albumin a few white blood cells an occasional red blood cell and a few granular and hyaline casts The hemoglobin was 11 gm leukocyte count 40 000 with 5% myelocytes 12% juvenile neutrophils 65% segmented neutrophils and 14% lymphocytes Blood serologic test for syphilis was negative Three blood cultures were sterile Agglutinations for *Pasteurella tularensis* were positive on two occasions in 1 40 dilution Brucella agglutinations and tuberculin tests were negative Spinal fluid was normal X rays of the lungs heart aorta esophagus stomach and duodenum as well as of the cervical spine were normal

The patient s temperature fluctuated between 102 and 104 On the 10th day she had pain in the right chest and a pleural friction was heard in the right axilla On the 14th hospital day she developed pain in the right flank The liver was palpated 4 fingerbreadths below the costal margin There was rebound tenderness X ray of the chest showed elevation of the diaphragm On the 30th hospital day laparotomy was performed There were fibrin deposits on the liver surface with an organizing peritoneal exudate Liver biopsy showed small focal areas of necrosis The post operative course was stormy with rise in temperature to 104 and in leukocyte count to 70 000

From the time of discharge until August 31 the patient was seen periodically The right breast was enlarged and edematous with a peau d orange appearance On October 6 a sinus developed in the right axilla with discharge of moderate amounts of pus

SUMMARY OF SECOND ADMISSION At the final admission temperature was 99 8 pulse 84 and respirations 24 with blood pressure of 116/74 There was a chain of large firm non tender lymph nodes along the posterior surface of the right sternocleidomastoid muscle On the right side of the chest in the anterior axillary line about 3 cm below the clavicle there was an ulcerated area 3-4 cm in diameter from which purulent material was draining The entire right axilla was involved in this massive abscess There was pitting edema of the right breast, with swelling extending over the right chest and shoulder anteriorly The lungs were clear The heart was normal The deep reflexes were hypoactive

Laboratory examinations showed hemoglobin 12 5 gm leukocyte count 27 240 Urine normal *Staphylococcus aureus* was grown from the draining abscess

The abscess was incised and drained with some improvement On October 26 an enlarged gland high in the neck was removed for histological examination (The report of the biopsy and the subsequent course of the illness were not revealed to the discusser)

DISCUSSION It seems clear from the distribution of the lymph node enlargement that the whole process in this case was not due to a local infection The pleuritis and also the abdominal manifestations must have a logical explanation It is unlikely that the inadequately treated syphilis or the tularemia could provide a satisfactory explanation of this final progressive illness which led to death within a period of about eight months

The key manifestation was the enlargement of the lymph nodes The most likely possibilities to be considered here are leukemia, Hodgkin s disease lymphosarcoma sarcoidosis and tuberculosis However, secondary carcinoma is a possibility The primary growth might have been in any one of several areas including tongue lip nasopharynx, esophagus, or some distant site The most common causes of unilateral enlargement of axillary glands are drainage of a local infection carcinoma of the breast, and lymphoma of some type

All diseases mentioned could be accompanied by fever but some information might be obtained from consideration of the blood picture showing a very high total white count and many young forms—described as leukemoid *Leukemoid blood pictures* may be seen in certain infections including tuberculosis certain intoxications such as eclampsia severe burns mercury poisoning or following a severe hemolytic reaction as after sulfonamide administration, in malig

nancy especially with bone metastases, and also in multiple myeloma and Hodgkin s disease

The fragments of liver tissue which were removed at operation showed scattered areas of focal necrosis This type of lesion might be caused by a variety of diseases some of which have already been mentioned such as tularemia actinomycosis tuberculosis and small necrotic tumor metastases This lesion suggests the addition of one possibility to the list in view of the history of polyarthritis the car diac murmur the pleurisy and prolonged fever—systemic lupus erythematosus It seems unlikely however that this could account for the striking local glandular enlargement

In considering these possibilities it may be noted that in tularemia a discharging sinus may develop as long as 24 months after the acute adenitis but here the interval was 60 months and in addition the ag glutination titre for *Pasteurella tularensis* was low Reactivation of an old infection after this interval of time seems unlikely Actinomycosis might be considered but this would be an unusual location for the initial lesion and one could not readily relate the occurrence of axil lary and cervical enlargement in a disease which spreads primarily by direct extension Tuberculosis seems unlikely One would not expect such a severe systemic reaction without more evidence of widespread involvement The lungs were free of disease by x ray and the tuber culin reaction was negative It seems more likely that any infection in this case was a secondary factor and that some type of malignant tumor was the primary disease

Leukemia seems ruled out by the failure of abnormal cells to appear in greater abundance the lack of any splenic or general lymph node enlargement or a more significant degree of anemia As between Hodgkin s disease and lymphosarcoma the latter seems more prob able in view of the localized nature of the lymphatic involvement and the absence of splenomegaly

The final choice must lie between lymphosarcoma and some other type of malignant tumor If this was a carcinoma the most likely primary site was the breast The lung might be suggested by the pleurisy but there was nothing else to support the possibility From the description of the progress of the axillary lesion and of the ulcer which was present carcinoma primary site undetermined seems the best diagnosis

ANATOMICAL DIAGNOSIS (Autopsy No 18212) Peculiar tumor (non pigmented melanoma ? monocytoma ?) involving right breast right

axilla and regional lymph glands metastases to supraclavicular lymph nodes parietal pleura and lung Large sloughing ulceration in right axilla Fat infiltration in renal tubules Lobular pneumonia Emaciation Recent upper quadrant laparotomy, right old lower abdominal scar Operative removal of uterus tubes ovaries and appendix Small corneal ulcer, left Polyp in colon

In the left upper lobe there was a tumor nodule 1 cm in diameter There was a large mass of tumor in the region of the breast on the right It ex tended through the fat and invaded the muscle and a large mass from the axilla showed similar invasion The tumor was necrotic in places

This tumor was composed of rounded though irregularly shaped cells that varied greatly in size and were not attached to each other In the great variation in size and shape of the nuclear masses and in the separate ness of the cells the tumor resembled a monocytoma Some of the larger cells were perhaps compatible with melanoma cells There was only the most delicate stroma to which the cells bore little relation They were not attached in lines along the stroma framework

SUMMARY This 46-year old Negro woman entered because of a draining mass in the right axilla She had had secondary syphilis inade quately treated at age 36 and ulcero glandular tularemia with the primary lesion on a finger of the right hand five years later Seven months before death she developed a tender mass in the right axilla with fever chilly sensations and leukocytosis She later developed pain in the right flank and a pleural friction rub The liver became palpable and abdominal tenderness with elevation of the diaphragm was noted At laparotomy there were fibrin deposits over the liver and an organizing peritoneal exudate The breast was enlarged and edematous with a peau d orange appearance and a sinus developed in the right axilla The final choice in differential diagnosis lay between lymphosarcoma and some other type of malignant neoplasm At autopsy a peculiar tumor was found involving the right breast and regional lymph nodes with metastasis to the supra clavicular nodes and the left pleura and lung It was thought to be either a NON PIGMENTED MELANOMA or a MONOCYTOMA



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Chapter 10

FEVER OF OBSCURE ORIGIN

THE MEASUREMENT of body temperature was one of the first precise quantitative methods to be applied in the study of disease Even before the occurrence of this important development the differential diagnosis of fevers had been for over 2 000 years a subject of consuming interest to physicians The methods which have been developed for the detection of specific infectious agents and their immunological products have done much to clarify the subject Nevertheless fever of obscure origin is still frequently encountered and it may present some of the most challenging and vexing problems that the clinician is called upon to solve The solution of some of these problems has been rendered more difficult in recent years by the introduction of therapeutic agents which may mask the true clinical picture either by causing temporary defervescence or by inducing a febrile sensitivity reaction

In this chapter particular attention will be paid to those cases in which fever persists for weeks or months without satisfactory explanation in spite of careful investigation But before going on to a consideration of these cases it may be well to recall that low grade fever is not always of pathological significance The body temperature may rise above normal during exercise or excitement particularly when the environment is warm Almost every practicing physician has encountered at least a few patients who appear to be in perfect health but whose temperature is repeatedly found to be about one degree above the normal average Reimann has applied the term habitual hyperthermia to a group of patients usually young females who exhibit over a period of years slight elevations in temperature up to 100 5

As in the study of other conditions it is helpful to make a systematic approach to the differentiation of obscure fevers The causative factors are so varied and numerous that it is difficult to con

struct any fully inclusive practical classification of febrile diseases A relatively simple classification of the causes of fever is shown in Table 15

Table 15 Causes of Fever

I Bacteremia
- A Staphylococcus
- B Streptococcus (including *Streptococcus faecalis*)
- C Coliform group
- D Others

II Localized infections
- A With abscess formation such as
  1. Suppurative pylephlebitis
  2. Appendiceal abscess
  3. Renal carbuncle
  4. Hepatic abscess
  5. Subdiaphragmatic abscess
  6. Empyema
  7. Psoas abscess
  8. Brain abscess
  9. Lung abscess
  10. Perinephric abscess etc
- B Without abscess formation such as
  1. Encephalitis
  2. Meningitis
  3. Pneumonitis
  4. Hepatitis
  5. Cholecystitis
  6. Pancreatitis
  7. Colitis
  8. Phlebitis etc

III Specific infections such as
- A Typhoid and paratyphoid fevers
- B Rickettsial infections
- C Tuberculosis
- D Syphilis
- E Tularemia
- F Brucellosis
- G Tetanus
- H Histoplasmosis
- I Malaria
- J Amebiasis
- K Bacterial endocarditis etc

IV Toxic and allergenic agents
- A Allergenic drugs (sulfonamides penicillin iodides etc)
- B Foreign proteins (horse serum etc)
- C Bacterial products (typhoid vaccine etc)

D Products of tissue death
   1 Myocardial infarction
   2 Pulmonary infarction
   3 Gangrene of extremity
   4 Necrosis of tissue elsewhere with associated sterile inflammation
   5 Accumulation of blood in body cavities or intestinal tract

V Diseases of the blood forming organs and lymph nodes
   A Leukemia
   B Infectious mononucleosis
   C Aplastic anemia
   D Pernicious anemia
   E Lymphomas

VI Malignant tumors
   A Carcinoma of the lung and pleura
   B Hepatic carcinoma
   C Hypernephroma etc

VII Mesenchymal or collagen diseases
   A Rheumatic fever
   B Rheumatoid arthritis
   C Systemic lupus erythematosus
   D Periarteritis nodosa
   E Dermatomyositis

Fever may appear in numerous other conditions such as heart failure hyperthyroidism heat stroke and cutaneous disease or con genital absence of the sweat glands with resulting disturbance of the normal mechanisms for dissipation of body heat The cause of the fever in these conditions is usually obvious and in most instances the abnormal temperature is not the central feature which calls for diag nostic study

BACTEREMIA

It is now considered good practice to obtain blood cultures in all cases of protracted and unexplained fever A single culture inoculated on ordinary media does not always suffice Both aerobic and an aerobic cultural conditions should be employed and the cultures should be incubated for at least two weeks to permit recognizable growth of the slow growing organisms such as the Bacteroides group It is preferable to obtain the blood for culture when the tempera ture curve is approaching its daily peak or at several intervals dur ing the day At least three cultures should be obtained on different days if there is good reason to suspect bacteremia

Gonococcal bacteremia is frequently overlooked owing to the diffi

culty of cultivating the organism even when all of the precautions mentioned above have been observed Gonococcal endocarditis may give rise to a fulminating illness with frequent wide swings in temperature In some cases it may produce a characteristic temperature curve with two distinct high peaks on each of successive days But the cases that are most likely to go unrecognized are those characterized by a relatively long apparently benign course, with low grade fever and little or no leukocytosis Such cases are not uncommon and they are most likely to escape attention if the gonococci have lodged on normal aortic cusps

Whenever it is feasible and safe to do so the use of antibiotics in cases of obscure fever should be withheld until after the blood cultures have been obtained Otherwise the correct diagnosis may never be made and the illness may continue and may even terminate fatally before effective therapeutic measures can be instituted Effective treatment may depend upon the isolation of the organism and the determination of its sensitivity to various antibiotic agents In cases of unrecognized bacterial endocarditis small amounts of penicillin may rid the blood stream of the bacteria and there may be a long delay before positive blood cultures can be obtained and adequate therapy instituted

LOCALIZED INFECTIONS WITH OR WITHOUT ABSCESS FORMATION

This relatively common cause of unexplained fever is familiar to most physicians But even when one is fully aware of the possibility and when fluctuating fever and marked leukocytosis point strongly toward a localized suppurative process it may be very difficult to locate the site of the infection For example a perinephric abscess may grow to relatively large size without causing pain or other localizing signs Its presence may not be discovered until it suddenly ruptures into a neighboring structure Abscesses of the liver may also escape detection The primary type of bacterial liver abscess is usually caused by an anaerobic streptococcus Amebic abscess of the liver, occurring in the absence of symptoms of amebic involvement of the colon may be a very deceptive cause of fever Infection of the urinary tract is a common cause of long-continued or recurrent fever especially in women This may be the case even though only a few pus cells can be found in catheterized specimens of urine In all cases of unexplained fever urine cultures should be made If the cultures are negative and urinary tract infection is still considered possible pyelo-

graphic studies should be made Hydronephrosis with low grade infection may exist in the absence of pyuria and positive cultures

There is too frequently a tendency to attribute long continued unexplained fever to so called hidden foci of infection such as chronically infected tonsils or adenoids appendix or gallbladder even when there is no direct evidence of disease of these organs It is of course true that local infections in these and other organs may under appropriate circumstances give rise to fever But in the absence of evidence of local disease it is rarely desirable to excise organs or tissues in the hope that this may be the solution to the problem in hand For example peridontal abscess may be the cause of unexplained fever and when such an abscess is discovered it should be attended to On the other hand it is rarely beneficial to resort to multiple dental extractions in the absence of demonstrable suppurative disease

SPECIFIC INFECTIONS

When the characteristic manifestations of a specific infection have reached full development the diagnosis usually presents no serious problem However in the early stage of the infection or when the manifestations are atypical many problems may arise For example although the characteristic manifestation of meningococcal infections is meningitis the early manifestations are those of a bacteremia and the disease may run its entire course and may even terminate fatally without the development of meningeal symptoms Syphilis may occasionally be manifested by fever in the absence of any specific evidence of the infection On the other hand one should not be misled into attributing fever to syphilis merely because of a positive serologic test False positive tests for syphilis may be encountered in the course of other febrile diseases The effect of a therapeutic test with potassium iodide may be the only means of assessing the validity of the diagnosis Of all the chronic infections tuberculosis is most frequently disguised as an obscure fever Efforts to demonstrate the tubercle bacillus either by direct smear or cultural techniques are usually unrewarding in this type of case On the other hand the intracutaneous tuberculin test may provide valuable information A positive test is of diagnostic value only in infants and young children but a negative test is of value in excluding tuberculosis in patients of all ages If the test is performed with increasing concentrations of tuberculo protein persistently negative results provide strong evidence that the fever is not due to tuberculosis There are exceptions to this statement particularly in older individuals Brucellosis although not a common

disease in all localities must always be considered among the specific infections The diagnosis may be difficult to establish Repeated blood cultures may be made It may be helpful to obtain cultures several times during a single 24 hour period The brucella agglutination test may yield valuable information but it is important to be sure that the antigen is a sensitive one and that due consideration has been given to the prozone phenomenon It has been stated that of the specific infections brucellosis is the least likely to be associated with significant elevation of the erythrocyte sedimentation rate The typhoidal type of tularemia may be very difficult to diagnose The lack of a history of direct contact with rabbits should not be given too great weight for there are many other known vectors When the fever is accompanied by signs of bronchopneumonia and deep intoxication tularemia should be suspected Typhoid fever once a serious epidemic disease of urban populations, has almost been eliminated from our cities by improved methods of hygiene It is now most frequently encountered in rural areas where sporadic cases may go unrecognized until serious manifestations develop Malaria which was also a common cause of obscure fever in former years, has now been virtually eliminated in large sections of the country However recurrent malaria is still seen among military and civilian personnel who *have served in endemic malarial areas It may also be encountered* chiefly in sea ports among drug addicts the so called "main line shooters who through use of a common syringe, pass the organisms from one individual to another

TOXIC AND ALLERGENIC AGENTS

Many drugs now in common use chiefly the chemotherapeutic and antibiotic agents may give rise to a febrile reaction It is known that even such a simple substance as iodine may unite with body proteins to form a complex which is antigenic in nature Many of the more serious febrile reactions to drugs have the clinical characteristics of a hypersensitivity phenomenon The resulting anatomical changes may *be those of periarteritis nodosa Since in the treatment of complex* clinical problems several drugs may be administered simultaneously or in rapid succession it is often extremely difficult to determine which agent has been responsible for the reaction

The classic example of a febrile hypersensitivity reaction is the serum disease which follows injection of horse serum Depending *upon the sensitivity of the individual there is usually a delay of 5* to 10 days between the injection and the onset of the hypersensitivity

phenomena These may take the form of fever accompanied by urticaria or other types of eruption lymph node enlargement joint pain and swelling simulating rheumatic fever, and a wide variety of other manifestations A helpful guide to diagnosis is localized inflammation at the site of the original serum injection The local reaction which is red indurated painful, and pruritic may precede the generalized reaction and may be mistaken for a subcutaneous abscess Serum disease may exhibit a series of remissions and relapses for several weeks

The febrile reactions which follow the injection of certain bacterial products such as typhoid vaccine are not of the delayed serum disease type There is a local reaction usually within 12–24 hours accompanied by fever which rarely lasts more than 48 hours

In the delayed anaphylactic hypersensitivity reaction which is the most common type seen with various therapeutic agents such as penicillin the sensitization may have occurred months or years previously In this event readministration may produce a reaction in a matter of hours rather than days The febrile reaction may be the only detectable clinical evidence of the allergic response

Febrile reactions varying in intensity from mild to severe may result from the death of tissue and absorption of degradation products A familiar example of this is the fever which accompanies myocardial infarction Likewise the accumulation of blood in the tissues or body cavities may provoke a febrile reaction High fever often fluctuating in type may occur in patients when old blood has accumulated within the gastrointestinal tract following a hemorrhage

DISEASLS OF THE BLOOD FORMING ORGANS AND LYMPH NODES

The more severe types of anemia are frequently accompanied by fever This is particularly true in pernicious anemia and sickle-cell anemia during relapses and in aplastic anemia In cases of leukemia myeloma lymphosarcoma and Hodgkin s disease there may be no clinical manifestation other than fever The successive waves of fever seen in cases of Hodgkin s disease so called Pel Fbstein fever may simulate the undulant fever of brucella infections In both Hodgkin s disease and lymphosarcoma fever may precede by many months the development of palpable glandular or splenic enlargement In cases of Hodgkin s disease in which the abdominal lymph nodes are primarily affected the illness may run its entire course as an unexplained fever

MALIGNANT TUMORS

The importance of fever as a manifestation of malignant tumors seldom receives the emphasis which it deserves It is of practical significance that fever may accompany primary growths and is not always to be taken as an indication of metastasis or secondary infection An example of this type encountered some years ago was that of a young man who had a long continued high grade fever The one positive physical finding was a moderately enlarged spleen The diagnoses entertained included various types of infections lymphosarcoma and Hodgkin's disease The spleen was removed at operation and the enlargement was found to be due to a primary sarcoma Following the operation the fever subsided The patient sub equently died of a postoperative complication At autopsy no tumor metastases could be found Certain types of tumors are particularly likely to produce fever This is true ot growths originating in the pleura and lungs and of those arising in the liver and biliary tract Tumors of the kidney which are frequently difficult to discover because of their hidden position, may give no indication of their presence other than fever

In some cases the fever associated with neoplasms may be accompanied by quite marked elevations in the leukocyte count and an eosinophilia In a case of long continued unexplained fever with leukocyte counts running up to 40 000 autopsy disclosed an adenocarcinoma originating in the tail of the pancreas We have encountered several cases of carcinoma of the nasopharynx with spread to the cervical lymph nodes in which there was both a marked leukocytosis and a considerable increase in the percentage of eosinophils

MESENCHYMAL OR COLLAGEN DISEASE

There is general familiarity with the constitutional manifestations which often accompany rheumatic fever in the absence of clinically detectable involvement of the joints or heart It is also well known that systemic lupus erythematosus may run its entire clinical course to a fatal termination without the appearance of any lesions of the skin In both of these diseases fever of high degree may be the presenting sign and may persist for many weeks before other manifestations appear Periarteritis nodosa has become increasingly familiar as a cause of fever The fever may be accompanied by rather rapid loss of weight and a leukocytosis Manifestations which should lead one to suspect periarteritis are renal involvement with hypertension, eosino-

philia peripheral neuritis and asthma These may occur singly or in various combinations

CHILLS

A chill may develop at the onset or during the course of many diseases and its occurrence may have important significance for diagnosis As pointed out by Perera there is no clear cut separation from the minor degrees of shivering and chilliness which may be due to similar causes but the use of the term chill should be applied to the combination of a subjective perception of inward trembling or actual cold and a usually generalized involuntary muscle tremor visible as an objective sign Chills may be seen in almost any type of infectious process whether bacterial viral parasitic rickettsial or due to a toxin but they are characteristically associated with a period of rapid and widespread invasion of the host As recorded in Table 16 a single

Table 16 Diseases Associated with Chills

I *Diseases in which a chill is often a prominent symptom at onset*
- A Lobar pneumonia
- B Tularemia
- C Leptospirosis
- D Influenza
- E Erysipelas
- F Bubonic plague
- G Acute hemolytic crisis
- H Osteomyelitis
- I Puerperal sepsis
- J Typhus fever

II Diseases in which repeated chills may occur
- A Septicemia
- B Abscess formation
- C Intermittent biliary duct obstruction
- D Phlebitis (pylephlebitis pelvic thrombophlebitis lateral sinus thrombosis)
- E Subacute or acute bacterial endocarditis
- F Brucellosis
- G Rat bite fever
- H Neoplasms (lymphoma leukemia hypernephroma)
- I Repeated use of antipyretic drugs in a patient with sustained fever
- J Malaria
  - 1 Natural vector
  - 2 Human transmission
    - a malaria inoculata
    - b main line shooter

chill is associated with many types of illness In those situations in which multiple chills develop as a result of the natural biological cycle of the parasite spread of infection or the development of a

complication such as a localized abscess or blood stream invasion this complex reflex takes on a greater significance from the standpoint of diagnosis

COMMENTS ON DIAGNOSTIC METHODS

Since the accurate diagnosis of febrile diseases involves the use of many laboratory procedures it seems appropriate at this point to comment upon the interpretation of laboratory data In no other field of medicine is it more important to have a clear understanding of the limitations of the techniques employed As a prime consideration no laboratory method can be expected to yield trustworthy results unless it is subjected to frequent tests of accuracy Samples may be mixed media may become contaminated and standards and stains are subject to deterioration Scientific data are usually considered to be unacceptable unless determinations are performed in duplicate or triplicate Multiple determinations are usually not feasible in clinical laboratories and for this reason the reported results cannot always be trusted unless they are confirmed by subsequent test If the finding is of crucial significance—as it is, for example in the case of a positive serologic test for syphilis—repetition of the test is obligatory

Even when the technical performance of laboratory tests is above reproach, their interpretation requires experience and judgment For example the interpretation of agglutination reactions in these days of multiple prophylactic vaccinations requires both judgment and a thorough understanding of immunological principles In attempting to arrive at a diagnosis of brucellosis one must be aware of the significance of the prozone phenomenon and of the deceptive nature of the skin reaction to brucella antigen Further one must realize that in order to recover brucella from the blood it may be necessary to make blood cultures at frequent intervals even at hourly intervals for a period of several hours

The use of therapeutic tests is of little diagnostic value unless the tests have been properly timed and have been planned in such a way as to yield a convincing result Therapeutic tests should not be attempted until after the basic diagnostic studies have been completed If bacterial endocarditis is suspected multiple blood cultures should be made before the therapeutic test Examples of febrile diseases in which therapeutic tests may be required are syphilis and amebic liver abscess To arrive at a diagnosis of syphilis the test should be made with potassium iodide or arsenicals Syphilitic fever would also be

expected to respond to penicillin but the defervescence would be of no diagnostic significance owing to the broad spectrum of activity of this antibiotic agent The response of the fever to administration of emetine in cases of amebic abscess of the liver is one of the most helpful and clear cut therapeutic tests available

The decision on whether to employ biopsies or exploratory laparotomy as diagnostic procedures also requires experience and good judgment Aspiration of sternal bone marrow is a simple procedure and it may yield valuable information particularly in disclosing the presence of abnormal cells However if one wishes to determine the state of activity of the bone marrow a surgical biopsy is much less likely to give misleading information than is an aspirated specimen Exploratory laparotomy should be employed only after other diagnostic methods have failed to solve the problem When the bacteriological and serological studies have yielded negative results when appropriate therapeutic tests have been negative when biopsies of the bone marrow and accessible lymph nodes fail to give a clue and when x ray studies of the lungs and bones disclose nothing of significance the cause of the fever is usually tuberculosis Hodgkin s disease or lymphosarcoma one of the collagen diseases or a hidden neoplasm In all of these conditions the active focus may be concealed within the abdominal cavity or in the retroperitoneal area An exploratory laparotomy may afford the only chance of making a diagnosis early in the course of the disease Otherwise one may lose the opportunity to carry out effective treatment Exploratory laparotomy may disclose unsuspected acute inflammatory lesions as well as the chronic diseases mentioned above For example cases of biliary tract disease have been described in which intermittent fever was the only symptom There was neither jaundice nor pain and the cholecystograms revealed no stones Nevertheless an exploratory laparotomy disclosed calculi in both the cystic and common bile ducts

Illustrative Cases

I

(#41106 Admitted Jan 9 1932 Died Jan 16 1932)

THIS 25 year old white male was admitted complaining of chills pain in the epigastrium and fever In June and October 1931 he had attacks similar to the one described in the present illness but between these episodes he felt well *The first attack of pain came on after eating* sausage and sour potatoes He felt a little sick after this and the following day had severe cramplike pain in the epigastrium which doubled him up The pain was aggravated by respiration

On January 2 1932 he developed a severe pain in the epigastrium likened to a ball of gas It was aggravated by respiration and he developed cough with yellow sputum He was anorectic and constipated Vomiting was induced for relief of pain On January 3 and 4 he felt better with less pain which however recurred on the night of the 4th only to subside again On that day he had a severe chill and from then on noted fever

PHYSICAL EXAMINATION on admission T 106 P 124 R 24 BP 100/55

The patient was perspiring profusely He had numerous herpetic lesions on the lips Over the hands and in the left axillary fold as well as on the back were small reddish areas with a central hemorrhagic spot and an areola which faded on pressure Fundi showed blurring of the disc margins The heart and lungs were normal There was no lymphadenopathy The abdomen was symmetrical There was tenderness on pressure high in the epigastrium in the mid line The liver was palpable at the costal margin The spleen and kidneys could not be felt and no masses were made out The genitalia were normal Rectal examination showed no abnormalities and neurological examination was normal

COURSE IN THE HOSPITAL The temperature fell rapidly to 101 and on the second day rose again to 105 On the third day it went from 100 to 103 and for the next six days was normal rising again to 104 on the day of death The white cell count remained at 15 000–16 000 He vomited bile stained material several times daily He was icteric Epigastric pain was intermittently present On January 15 he looked more icteric and had oliguria He was irrational and the blood pressure was 88/42 Tenderness

developed in the right flank in addition to that in the epigastrium and he complained of shoulder discomfort On bimanual palpation fluctuation was described in the right costovertebral area On January 16 he was comatose with acidotic respirations Catheterization produced 2 ml of urine loaded with casts

LABORATORY DATA Blood serologic test for syphilis was negative hemoglobin 85% leukocytes on admission 55 000 with 96% polymorpho nuclear cells 3% myelocytes Urine had a specific gravity of 1 020 acid reaction albumin 1 plus occasional white cell no red cells occasional granular cast Blood culture sterile Urine culture sterile Stool normal Nonprotein nitrogen (Jan 11) 42 mg % sugar 117 mg % bilirubin 2 3 mg % On January 15 nonprotein nitrogen was 132 mg % van den Bergh prompt biphasic with total 4 4 mg % sodium chloride 360 mg %

X ray examination of the chest on January 11 showed lungs clear On x ray of the abdomen it was thought the left kidney might be a little larger than normal but there was no evidence of calculus

DISCUSSION A number of physicians saw this patient and all were impressed by the fever and intense leukocytosis as well as by the paucity of physical alterations which might indicate the nature of his illness The diagnosis must depend on proper interpretation of the manifestations described and particularly on the course of the illness

The outstanding features of this case were chills fever leukocyto sis vomiting abdominal discomfort at first intermittent and then continuous jaundice and finally anemia The only evidence of local ization was afforded by the epigastric pain which had occurred in several episodes over a period of six months and had been both the initial complaint and a recurring manifestation of the final illness It would seem that the diagnosis should provide a satisfactory ex planation not only of the last brief illness but of the recurring episodes which preceded it

The only blood culture which was made was not inoculated on any special media so the fact that it was sterile does not exclude bac teremia In view of the repeated attacks over a period of 6 months it would seem unlikely that this was basically a recurrent bacteremia but there may have been blood stream invasion in the final stages of the illness

In view of the recurrent symptoms one must strongly consider gastric or duodenal ulcer with final perforation and a localized ab- scess in the right upper quadrant appendicitis with the development in the final attack of pylephlebitis or a liver abscess gallbladder dis ease with empyema or a walled off perforation with infection outside of the biliary tract or extending into the liver acute pancreatitis renal carbuncle intermittent obstruction of the ureter due to some

the vessels was there any thrombosis of the mesenteric veins or of the main portal vein or its larger extrahepatic branches In the liver it was possible to demonstrate thrombosis of the branches It seemed clear that the production of the abscesses in the liver was due to infection reaching it by way of the portal vein

SUMMARY This 25 year old *white male had two attacks of epigastric* pain with vomiting during the 6 months before admission One week before a similar pain developed but abated and two days later he had a chill following which there was high fever On examination he had fever labial herpes icterus hemorrhagic spots on the arms and back blurring of the optic discs tenderness on pressure high in the epigastrium and a *palpable liver at the costal margin There was persistent leukocytosis* with shift to the left He later developed hypotension oliguria and uremia It seemed most likely that the final illness was due to APPENDICITIS and PYLEPHLEBITIS WITH LIVER ABSCESSES This was confirmed at autopsy

II

(#228257 Admitted December 26 1945 Died January 9 1946)

THIS 23 year old Negro housemaid was admitted with dyspnea nausea and vomiting She first noticed dyspnea on exertion in 1938 and was told that she had a leaky heart In May 1941 she became pregnant Physical examination at that time revealed a vigorous precordial impulse in approximately normal position A definite presystolic thrill was present at the apex the first sound was accentuated there was a presystolic crescendo rumble and a high pitched systolic murmur loudest in the left anterior axillary line Over the base there was a loud blowing diastolic murmur maximum in the second left interspace and transmitted down the left sternal border The pulmonic second sound was increased in intensity The pulses were collapsing in quality The Wassermann test was negative X ray of the chest showed increase in the transverse diameter of the heart the left border was straight with prominence in the region of the pulmonary arteries The lungs were clear The pregnancy terminated in delivery of a normal child During the next few years there was little change in the patient s condition

During 1945 there was an increase in her dyspnea Early in December 1945 she began to have some nausea and vomiting Her heart was found to be larger than before and the urine showed large amounts of albumin

PHYSICAL EXAMINATION on admission T 100 2 P 100 R 24 B P 140/90

The patient looked only mildly ill and there was no jaundice cyanosis or pallor The fundi were normal There was no lymph node enlargement The veins in the neck were distended The lungs were clear to percussion and auscultation The heart was found to be greatly enlarged to the left and to the right with the point of maximal impulse in the mid axillary line There was a marked precordial thrust and a systolic thrill at the apex accompanying this there was a loud presystolic murmur and a systolic bruit There was a diastolic murmur along the sternal border The pulmonic second sound was increased in intensity There was a gallop rhythm The liver was palpated 3 fingerbreadths below the costal margin There was no edema

COURSE IN THE HOSPITAL The patient s fever became more marked reaching 104 on occasions before her death There was a marked tachycardia The dyspnea and evidence of cardiac failure responded well to therapy Three days after admission she became psychotic It was thought that the various medications might be contributing to this hence all drugs were discontinued Numerous examinations were done in an effort to find

the cause of this psychosis Various bacteriological tests lumbar punctures and neurosurgical consultation brought nothing to light A leukocytosis developed which with her fever led to the administration of penicillin This did not seem to have any effect On the morning of January 9 the patient s condition was apparently the same as it had been for the previous week One half hour later she was found dead

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin 14 gm Leukocyte count on admission 8 600 on December 31 11 400 and on January 4 25 000 with 8% juvenile neutrophils 76% segmented neutrophils 10% lymphocytes and 12% monocytes Nonprotein nitrogen was 38 mg % CO_2 combining power 25 8 mEq chloride 92 6 mEq Urine on admission had a specific gravity of 1 010 albumin 4 plus and innumerable white and red blood cells later occasional white and red cells and granular casts were found

Cultures of the throat showed no pathogenic organisms Blood cultures on several occasions were sterile Urine cultures showed *Staphylococcus albus* On x ray examination the heart was enlarged and the left border of the cardiac silhouette was straight The lungs were clear

Electrocardiogram showed slight right axis deviation and a rate of 103 P waves in Lead II were enlarged The record suggested auricular enlargement and possibly right ventricular preponderance

Lumbar puncture revealed normal fluid under no increased pressure

DISCUSSION Two major problems present themselves for interpretation in this case

(1) The nature of the heart disease

(2) The cause of the febrile illness with leukocytosis and acute psychotic manifestations which preceded death

(1) When this patient was first seen the heart was normal in size and signs of both mitral stenosis and aortic insufficiency were present the aorta being normal in size The serologic test for syphilis was always negative It seems likely that rheumatic fever was the basis of the aortic valve lesion and if one accepts a rheumatic basis for the aortic lesion there is ample reason to believe that the mitral valve was involved by the same process

(2) The most important objective finding was the unexplained high fever associated with leukocytosis Vegetative endocarditis must always be considered in a patient with valvular heart disease and unexplained fever No systemic embolic phenomena and no pulmonary lesions were noted Also several blood cultures were sterile there was no appreciable anemia and the spleen was not palpable Occasionally one sees a diffuse encephalitis associated with small cerebral emboli which may result in a clinical picture suggestive of general paresis or encephalitis due to other causes

There were no manifestations here suggestive of local abscess formation other than the possibility of a brain abscess but the patient complained of no headache there were no evidences of increased intracranial pressure and no localizing neurological signs There was no evidence of a localized infection without abscess such as pyelitis or meningitis with the possible exception of an acute encephalitis

Two specific infections seem worthy of mention tuberculosis and rheumatic fever Miliary tuberculosis cannot be ruled out with certainty but the very high leukocyte count is against it

Rheumatic fever can produce a picture simulating encephalitis The sudden exacerbation of the cardiac manifestations might have been associated with rheumatic activity and the leukocytosis is explainable on this basis but there was no history of a preceding infection and none of the other classic features of an acute rheumatic state were observed

Some disease of the blood forming organs such as lymphoma and leukemia must always be considered as a possible cause of unexplained fever but there was no evidence here to suggest the presence of any of these diseases

Malignant tumors may cause fever Forty to 50 per cent of all tumors especially those of the abdominal organs and primary neoplasms of the liver kidneys and bronchi and pleura are accompanied by fever The changes in the urine which failed to clear up entirely with improvement of the heart failure might arouse suspicion of a renal neoplasm but the facts to support such a possibility are meager

All drugs were stopped in this case with no change in the patient s condition There was no evidence to suggest pulmonary or myocardial infarction except for the possibility of a terminal pulmonary embolus

Cerebral emboli may have been present if the patient had bacterial endocarditis or old mural thrombi on the left side of the heart

Heart failure itself may be accompanied by fever but almost never to the degree seen in this case and at the time of death the cardiac insufficiency had responded moderately well to treatment

From the various categories into which the possible explanations for fever of unknown origin fall several possibilities have been singled out which must be considered in more detail

(1) Bacterial endocarditis with cerebral emboli,

(2) Brain abscess

(3) Tuberculosis
(4) Acute rheumatic fever
(5) Acute encephalitis
(6) Mural thrombi with cerebral embolism

For reasons already given brain abscess and tuberculosis seem very unlikely explanations There were none of the localizing neurological signs usually seen in the various types of acute encephalitis so that we are left with

Bacterial endocarditis
Acute rheumatic fever
Cerebral emboli from mural thrombi

We may review the positive findings briefly and see which of these possibilities offers the best explanation of them

The illness began with increase in dyspnea nausea vomiting fever with leukocytosis followed by an acute delirium, and a great increase in the size of the heart There were changes in the urine with hematuria The fever did not decrease with penicillin administration Blood cultures were repeatedly sterile An acute exacerbation of rheumatic fever seems most likely

ANATOMICAL DIAGNOSIS (Autopsy No 19763) Chronic rheumatic endocarditis of tricuspid mitral and aortic valves Mitral stenosis Healing bacterial vegetation of aortic and mitral valve Hypertrophy left auricle and right ventricle Chronic passive congestion of lungs liver and pancreas Small hemorrhages in lung Marked extramedullary blood formation in spleen hyperplasia of femur marrow Acute tonsillitis Calcified primary tuberculosis lesion in right upper lobe of lung Calcified hyaline tubercles in lymph nodes Medial cystic degeneration of aorta

The heart was hypertrophied The leaflets of the mitral valve were fused together and there was great stenosis The mitral valve was thickened and cartilaginous and several rather large firm masses of prominent material roughened it There was a large necrotic vegetation in the sinus of Valsalva of the left aortic cusp which had ruptured through All areas of the brain appeared grossly normal no emboli were found on repeated sectioning

Mitral valve sections showed scarring and calcification but also a fibrinoid vegetation that was undergoing organization The section of the aortic valve showed similar alterations There were no lesions in the myocardium or lining of the left auricle suggestive of rheumatic fever Spleen was remarkable in that it contained a phenomenal amount of extramedullary blood formation Liver showed very marked chronic passive congestion

SUMMARY This 23 year old Negro girl was found to have valvular heart disease four years before death with evidence of mitral and aortic involvement One month prior to death she developed nausea increased dyspnea further cardiac enlargement and albuminuria Examination

revealed fever cardiac enlargement signs of aortic and mitral disease a gallop rhythm and hepatomegaly She ran a high fever with leukocytosis and became psychotic There was no favorable response to penicillin She died suddenly The two main possibilities were acute exacerbation of rheumatic fever or chronic rheumatic heart disease with superimposed bacterial endocarditis All blood cultures were sterile Autopsy revealed chronic rheumatic heart disease with healing BACTERIAL ENDOCARDITIS on the mitral and aortic valves

III

(#523195 Admitted December 8, 1949 Died February 15 1950)

THIS 74 year old white man entered complaining of weakness and of fever of two months duration At age 20 he had had inflammatory rheumatism Several examinations for life insurance the last being 10 years before death had revealed no abnormalities There had been some stiffness of his fingers for four years

He was in good health until eight weeks before admission when he developed generalized weakness and a low grade fever Some mental confusion was noted and on occasions he had generalized aching He had lost 10 pounds in weight

PHYSICAL EXAMINATION on admission T 99 4 P 80 R 20 B P 130/60

The patient was a well preserved elderly man who appeared quite depressed The skin was rather loose Extraocular movements were well performed and the fundi were normal There was redness of the pharynx There was no venous distention There were a few small lymph nodes in the inguinal regions and axillas The lungs were clear The heart was slightly enlarged The point of maximal impulse was 10 cm from the midline in the 5th interspace The sounds were normal A systolic murmur was heard over the lower precordium and in the back A soft systolic murmur over the aortic area was transmitted to the vessels in the neck The liver and spleen were not enlarged The prostate was enlarged There was slight thickening of all of the peripheral vessels Sensory examination was normal Strength was poor generally The reflexes were active

COURSE IN THE HOSPITAL The patient ran an irregular fever with temperature ranging up to 102 rectally Occasionally the temperature remained as low as 100 sometimes for a week During the early part of his stay he lost weight but during the last two weeks dependent edema accumulated On several occasions tenderness was noted over localized areas of the calf No petechiae were found and the fundi remained normal On December 21 he was started on a course of penicillin (900 000 units a day for one week) On January 21 an alpha *Streptococcus mitis* was grown from the blood This was the only positive culture of numerous ones taken during his hospital stay This organism was insensitive to penicillin but moderately sensitive to Aureomycin A few days after this culture was taken he was given 2 000 000 *units of penicillin 3 times daily plus* Benemid for five days On the third day of this therapy his temperature dropped below 100 and remained below for 12 days Because of the rising non

protein nitrogen and marked urinary frequency a Foley bag catheter was inserted on February 13 and 320 ml of clear urine was withdrawn *A aerogenes* was cultured from the urine The patient s azotemia had pro gressed in the face of a daily urinary output of about 1 000 ml On the evening of February 14 he developed bloody mucus in his mouth with no visible bleeding point That evening he became dyspneic with audible tracheal rhonchi and was semi stuporous Nail beds were cyanotic the neck supple and the extremities cold Heart sounds were rapid and faintly heard Blood pressure was 135/70 pulse rate 140 Abdomen was slightly distended He died the next day

LABORATORY DATA Blood serologic test for syphilis was negative Blood chemical examinations on admission showed nonprotein nitrogen 56 mg / sugar 80 mg / serum albumin 3 1 gm % and globulin 3 2 gm % alkaline phosphatase 2 7 units cephalin flocculation 1 plus thymol tur bidity 3 units There was a progressive rise in nonprotein nitrogen to 143 mg / Cephalin flocculation rose to 3 plus and thymol turbidity to 12 Smear was normal except for slight achromia The hemoglobin which was 13 gm on admission reached 8 5 grams by December 28 Leukocytes varied from 8 000 to 20 000 during his hospital stay with the same dif ferential count as given below

Urine examination showed a specific gravity of 1 020 sugar and albumin negative occasional white cells and casts Repeated urine examinations were done Red blood cells were found up to 50 per high power field and there were occasional fine and granular casts present There was albumin but never in large amounts

Agglutination reactions for typhoid paratyphoid and Brucella were negative A lumbar puncture was done and the spinal fluid was entirely normal Stools were negative for parasites Sternal puncture revealed no abnormal cells

On February 9 hemoglobin was 11 gm hematocrit 35 sedimentation rate 31 mm per hour icterus index 3 leukocyte count 14 600 with 3/ juvenile neutrophils 76/ segmented neutrophils 3/ eosinophils 1% basophils 9/ lymphocytes and 8% monocytes

Numerous x ray examinations were made that of the chest on December 9 showing heart and aorta within normal limits lungs clear except for a calcified focus There was no evidence of metastasis Both the thoracic and lumbo sacral spine showed a minimal amount of hypertrophic change with no evidence of metastasis On December 16 intravenous pyelogram showed both kidneys to be normal in size shape and position There was bilateral excretion but concentration of dye was poor Lower portion of left ureter appeared dilated On the same date barium enema revealed a diverticulum in the sigmoid colon A gastrointestinal series on December 19 showed normal esophagus stomach and duodenum

Muscle biopsy showed no specific lesions and a lymph node revealed only hyperplasia

DISCUSSION The problem here is the differential diagnosis of a febrile illness of several weeks duration which was accompanied by

loss of weight and very marked asthenia I first saw the patient about five weeks after admission and at that time it did not seem that this was any of the usual types of bacteremia, for in such a situation organisms are usually cultured from the blood stream without too great difficulty unless chemotherapy has previously been carried out Of the possible localized infections which might be present here, two seemed to deserve serious consideration (1) urinary tract infection and (2) subacute bacterial endocarditis Of the specific infections, the only one which had not been adequately ruled out at that time was tuberculosis There was no evidence that this prolonged illness was due to any toxic agent or a hypersensitivity reaction to any chemical agent Of the diseases of the blood forming organs Hodgkin's disease or lymphosarcoma seemed possible and at that time neoplastic disease in other locations had been largely ruled out It was still possible that the patient might have some type of collagen vascular disease Thus the major possibilities were

(1) Subacute bacterial endocarditis which had not been ruled out either by adequate numbers of blood cultures or by an adequate therapeutic test
(2) Tuberculosis—no gastric washings had been recorded and no tuberculin test had been done
(3) Hodgkin s disease or some other type of neoplasm
(4) Collagen vascular disease

It was suggested that further blood cultures be done that tuberculin skin tests be made and gastric washings cultured, that careful review of the eyegrounds for the presence of tubercles or cytoid bodies be made that the urine be checked repeatedly to see if there really was a mild hematuria and that repetition of the intravenous pyelogram be considered The low phenolsulfonphthalein output with rather good concentrating power was noted The azotemia and slight eosinophilia might have favored diagnosis of periarteritis nodosa but the renal picture was more compatible with that seen in subacute bacterial endocarditis particularly with a normal blood pressure Azotemia as a direct consequence of Hodgkin s disease would certainly be unusual All of the subsequent radiological examinations and tissue biopsies failed to reveal any evidence of a primary neoplasm or of Hodgkin s disease The spleen never became enlarged In view of these results and of the difficulty in explaining the renal picture one may safely rule out any primary type of blood dyscrasia Hodgkin s disease or a malignant neoplasm

Subsequent examinations were made for tuberculosis the tuber

culin tests were negative and again the course of the illness did not favor this diagnosis One would not expect so rapidly progressive an anemia with tuberculosis No lesions appeared in the eyegrounds nor any in the repeated examinations of the chest by x ray However tuberculosis may run a very atypical course in an elderly individual

The course of the illness had features compatible with systemic lupus erythematosus or periarteritis nodosa However there were never any cutaneous lesions or evidence of serous membrane involvement and although it is difficult to rule these diseases out the facts point more to the final possibility namely subacute bacterial endocarditis In the first place the major cardinal features of this disease are present prolonged fever progressive anemia in the presence of almost certain valvular disease of the heart and a positive blood culture for alpha *Streptococcus mitis* which although recovered only once seems unlikely as a contaminant In elderly individuals when bacterial vegetations are superimposed on a calcified aortic valve the illness may run a rather unusual course and there may be difficulty in culturing the organisms from the blood Embolic lesions are uncommon The eradication of the infection may require large amounts of antibiotic over a long period of time During the third day on penicillin the temperature returned to normal levels The progressive azotemia without elevation of the blood pressure is compatible with the glomerulonephritis of bacterial endocarditis Bacterial endocarditis is most often engrafted on a heart valve which has previously been damaged by disease or is the seat of a congenital lesion The findings were compatible with mitral insufficiency and aortic stenosis The history of arthritis was suggestive of rheumatic fever This is the most common disease which leads to valve deformity and subsequent development of bacterial endocarditis It is most likely that the vegetations were on the aortic valve placing the renal lesion on an embolic basis although a diffuse glomerulonephritis may develop in this situation It would explain the episodes of muscle tenderness and perhaps the periods of mental confusion if the anemia and azotemia plus arteriosclerosis were not sufficient to account for them The other possibilities are of course that the patient may have had calcific aortic stenosis or a congenital bicuspid valve or the infection may have attacked a normal valve but the evidence points to rheumatic endocarditis

ANATOMICAL DIAGNOSIS (Autopsy No 22223) Collagen vascular disease Periarteritis nodosa generalized healed and healing lesions and fresh necrotizing arteritis Chronic glomerulonephritis Cardiac hyper

trophy Hyaline and calcified vegetations on mitral and aortic valves Hypersensitive pneumonitis widespread pulmonary hemorrhage and edema Necroses in spleen and lymph nodes with abundant cellular infiltrations containing eosinophils Crystals in renal tubules Arterio sclerosis generalized Emphysema Prostatic hyperplasia Hypertrophy of bladder Cystitis cystica

This was a complicated case of collagen vascular disease with three predominating patterns—periarteritis nodosa glomerulonephritis and hypersensitive pneumonia The periarteritis and glomerulonephritis had been present for some time as indicated by the healed and healing lesions but the continuing fresh necrotizing arteritis and the fresh glomerular lesions showed there was no abating in the continuity or severity of these processes Healed vascular lesions with intimal proliferation organized thrombi and periarterial fibrosis were seen in the coronary and pulmonary arteries and in the wall of the gallbladder and about the adrenals It was interesting that vessels of all sizes were injured Similar lesions were seen in the kidneys independent of the glomerulonephritis Fresh arterial lesions were numerous in striated muscle adrenals testes periprostatic tissue pancreas and dura mater The most recent and severe arterial lesions were in the spleen where virtually every arteriole and artery were involved Plasma cells and eosinophils were especially conspicuous Focal necroses and infiltrating cells are seen in lymph nodes and the subcutaneous tissue There was diffuse glomerulonephritis which was chronic in that there was considerable replacement of nephrons by scarring but in all areas the continuing classic lesions of glomerulonephritis were present There was much hemorrhage in tubules and abundant interstitial cellular infiltration of plasma cells and eosinophils The actual cause of death was massive pulmonary hemorrhage This could have resulted from rupture of one of the larger necrotic intrapulmonary arteries or it could have been associated with the widespread thrombosis and necrosis in the alveolar walls The lesions of so called hypersensitive pneumonitis appeared to be most recent and likely were a precipitating factor in the patient s death

SUMMARY This 74 year old white man complained of weakness and unexplained fever of two months duration Examination revealed fever weight loss slight lymphadenopathy apical and basilar systolic murmurs with slight cardiac enlargement anemia and leukocytosis Fever persisted the anemia progressed uremia developed and transient muscle tenderness was noted Bloody sputum tracheal rales and cyanosis preceded death After consideration of the various causes of unexplained fever the most likely possibilities appeared to be collagen vascular disease and bacterial endocarditis The muscle biopsy was negative and one blood culture showed an alpha streptococcus Autopsy revealed calcified vegetations on the aortic and mitral valves but the basic lesions were those of collagen vascular disease manifested by PERIARTERITIS NODOSA GLOMERULONEPHRITIS and a terminal HYPERSENSITIVE' PNEUMONITIS In view of the widespread muscle and lymph node lesions at autopsy it is of interest that the biopsies were negative This emphasizes the limitation of this technique in which only a small sample of the total tissue potentially involved can be examined

IV

(#285259 Admitted February 23 1943 Died March 9 1943)

THIS 41 year old housewife was admitted complaining of pain in the chest dyspnea orthopnea and generalized weakness of nine weeks duration At age 15 she had been ill with loss of weight fever and night sweats Tubercle bacilli were found in the sputum She made a good recovery but at age 21 had a recurrence of the same symptoms lasting 6 months

In 1940 she developed intermittent attacks of diarrhea Her stools increased in bulk and a diagnosis of sprue was made She was placed on a diet with improvement In December 1942 she developed an acute febrile illness associated with an eruption on the forehead She had pleuritic pain in the left chest and general malaise X ray examination revealed a calcified area in the left apical region and thickening of the pleura at the left base She became more dyspneic and developed tachycardia fluid appeared in the left pleural cavity and peripheral edema and ascites as well Thoracenteses were done but no tubercle bacilli could be found

PHYSICAL EXAMINATION on admission T 102 P 130 R 30 B P 98/60

The patient was acutely ill with pallor and dyspnea There was edema about the waist but not over the sacral region or extremities A large shallow ulcer was found on the margin of the tongue The thyroid felt full and she complained of tenderness in this region Movement of both sides of the chest was limited the movement on the left being more limited than that on the right The percussion note was impaired over both lung bases being especially so on the right side where the tactile fremitus was markedly reduced There were numerous moist and crepitant rales over the right base Breath sounds were suppressed on the right and normal in character on the left where a few moist rales were audible The heart was thought to be a little enlarged The sounds were distant and a pleuro pericardial friction rub was heard along the left sternal border There was a systolic murmur audible at the base There was moderate ascites The spleen was greatly enlarged The liver edge could not be palpated

COURSE IN THE HOSPITAL The temperature remained between 102 and 104 with a parallel increase in pulse rate She gradually became stuporous and lapsed into coma A paradoxical pulse was noted Respirations ceased on March 9

LABORATORY DATA Blood serologic test for syphilis was negative red blood cells 4 million hemoglobin 13 gm hematocrit 37 2 sedimentation rate 1 mm per hour leukocyte count 5 750 with 89% segmented

neutrophils Blood nonprotein nitrogen 20 mg % chloride 96 9 mEq total serum protein 5 19 gm % albumin 3 25 gm % and globulin 1 94 gm % Urine examination showed 1 plus albumin 30 to 40 white blood cells and an occasional red blood cell per high power field Blood culture was sterile Sputum was negative on several occasions for acid fast organ isms as was material from the ulcer on the tongue

Electrocardiogram showed normal sinus rhythm and sinus tachycardia with the auriculoventricular conduction time at the upper limit of normal T1 and T3 were essentially isoelectric T2 was upright and T4F inverted

X ray of the chest showed the heart enlarged especially to the left the left border was straight The changes were compatible with pericardial effusion The lungs showed evidence of an old tuberculous process starting in the lower portion of each lung field

DISCUSSION The multiplicity of findings make it difficult to de cide on a starting point around which to assemble the diagnostic pos sibilities It is wise to list in chronological order the major facts to see clearly what must be explained

(1) Proved pulmonary tuberculosis at age 15 with recurrence at age 21
(2) At age 38 developed intermittent diarrhea diagnosed as sprue
(3) At age 41 acute febrile illness with pleural pain malaise Later dyspnea pleural effusion ascites and peripheral edema
(4) Physical examination reveals fever tachycardia tachypnea low pulse pressure dyspnea pallor tongue ulcer, thyroid full and tender dullness and rales both lungs, enlarged heart shadow, pericardial friction rub basilar systolic murmur ascites sple nomegaly
(5) No leukocytosis
(6) Continual high fever to death approximately 10 weeks after onset of final acute illness

After review of these facts it seems logical to list those causes of high fever with no leukocytosis which may be accompanied by peri carditis in the presence of normal nonprotein nitrogen These would be

(1) A pyogenic infection with purulent pericarditis
(2) Malignant neoplasm with invasion of the pericardium
(3) Disseminated tuberculosis
(4) Systemic lupus erythematosus

The high fever and the short course of the final illness are about all that suggest that this patient could have had a bacteremia with a purulent pericarditis It is hardly conceivable that this could have been an infection due to any of the common bacteria such as the

pneumococcus streptococcus or staphylococcus and run such a long course in the absence of any chemotherapy and without an elevated leukocyte count The tongue ulcer the high fever and the possible splenomegaly might suggest histoplasmosis but one would expect more anemia from a generalized infection of this type *Salmonella choleraesuis* infection in adults is usually engrafted on some under lying disease The absence of any localized abscess formation is against a bacteroides infection The rather acute onset and rapid progress of the disease as well as the diversity of the physical findings militate against a diagnosis of any of the mycotic infections

This could conceivably have been an atypical bacterial endocarditis with the fever slight anemia bizarre pulmonary and pleural mani festations and splenomegaly The only murmur was a systolic one at the base If a diastolic murmur had been heard one might give this possibility more consideration even with the sterile blood culture

Neoplastic disease with invasion of the pericardium must be con sidered This may present a clinical course very difficult to distinguish from tuberculous pericarditis Three possible primary sources of a neoplasm might be considered Carcinoma of the thyroid may metas tasize widely and could conceivably produce such a picture as this There was tenderness over the thyroid The most frequent tumor which may invade the pericardium is a bronchogenic neoplasm In that event it would be difficult to explain the abdominal findings unless there were metastases to spleen and also liver with possibly portal vein obstruction This would be unusual Equally unusual but offering an explanation of the left upper quadrant mass would be carcinoma of the stomach Such a tumor may invade the pericardium

There seems no question that this patient had pulmonary tuber culosis at the age of 15 It is difficult to believe that she could have had tuberculous enteritis as the cause of the intermittent diarrhea but there could have been I suppose tuberculosis of the cecum at that time Tuberculous enteritis usually appears in the presence of ad vanced pulmonary tuberculosis The final illness with high fever nor mal leukocyte count pleural effusion pericarditis and possible peri tonitis all could be explained by the diagnosis of tuberculosis as could the left upper quadrant mass if it represented say a large omental mass Likewise the ulcer of the tongue may have been tuberculous even though no bacilli were recovered from it

An equally convincing story can be made for systemic lupus ery thematosus This disease may be seen in individuals who have a tuberculous infection It may extend over a period of years with

exacerbations alternating with periods of remission lasting for several years In any given period of activity the signs and symptoms may be confined to a rather limited area of the body There may be for example a polyarthritis which subsides, a period of good health *then a pleurisy with effusion another free period and then a skin* eruption or pericardial effusion etc Abdominal symptoms with diarrhea are not too uncommon, but usually there is a bloody diarrhea and not a spruelike syndrome All of the manifestations of the final 10 weeks of illness are quite compatible with lupus except possibly the tongue ulcer Many patients with lupus have oropharyngeal ulceration There was also a vague story of facial eruption which had no specific features A large spleen might be expected more often in this disease than in tuberculosis Although there may be doubt about the splenomegaly the description rather suggests that the left upper quadrant mass was spleen and one observer described the splenic notch

ANATOMICAL DIAGNOSIS (Autopsy No 18278) Monocytic lymphosarcoma arising in tongue Extension of tumor in cervical tissues Widespread small metastases in esophagus adventitia of aorta pleura and *lungs epicardium and wall of left auricle diaphragm peritoneum* Fallopian tube lymph nodes and spleen Fibrinous pleurisy pericarditis and peritonitis Patchy bronchiectasis Chronic cystitis with cystitis cystica and squamous metaplasia Pulmonary edema Purulent bronchitis lobular pneumonia

The heart was atrophic The surface was covered with a fibrinous exudate Surface of left lung contained a great deal of fibrin and also some fibrous tags There was a calcified scar at the left apex There was an extensive degree of bronchiectasis in the lower part of the upper lobe and in the middle lobe of the right lung

Most of the symptoms can be related to a monocytic lymphosarcoma arising in the deep tissues of the tongue It had extended into the mucosa in several areas and in one place was covered by a large area of diphtheritic inflammation The tumor replaced large areas of lingual muscle and extended into the cervical tissues replacing muscle bundles in the neck The thyroid was surrounded by tumor but was invaded at only one small point The wall of the esophagus was partially replaced by tumor Fibrinous pleurisy pericarditis and peritonitis were produced by small nodules of tumor cells plugging lymphatics in the serosa covering the colon the diaphragm the pleura and epicardium Most interesting were large necroses in several lymph nodes in which shadows of large but no longer recognizable cells could be seen In the spleen there were numerous tumor cells There were patches of pulmonary edema a purulent bronchitis and numerous small areas of lobular pneumonia

SUMMARY This 41 year-old white woman had tuberculosis at age 15 with a recurrence at 21 Ten weeks before death she developed an acute febrile illness with a facial eruption and later dyspnea and edema Exami

nation revealed fever pallor a tongue ulcer a tender thyroid pulmonary abnormalities an enlarged cardiac shadow with a pericardial friction rub splenomegaly and ascites The leukocyte count was normal She ran a continual high fever The causes of such a fever without leukocytosis which might be accompanied by a pericarditis in the presence of a normal nonprotein nitrogen are reviewed A diagnosis of systemic lupus erythematosus was made but the cause found at autopsy was a widespread monocytic LYMPHOSARCOMA which had apparently originated in the tongue

V

(#313714 Admitted February 10 1944
Operation March 11 1944)

THIS 56 year old Negro female entered with pain in the right chest of 4 weeks duration

On December 24 1943 she developed chills fever and generalized malaise Severe sweating at night ensued She had had a mild head cold prior to onset of the severe symptoms After a few days all of these manifestations disappeared and she had no cough or chest pain Four weeks before entry she developed a sudden pleuritic type pain under the right breast A dull ache persisted which gradually decreased in severity She continued to feel short of breath and lost a good deal of weight

PHYSICAL EXAMINATION on admission T 102 4 P 104 R 24 B P 118/74

The patient had lost weight Respirations were shallow and she winced with pain on deep inspiration No jaundice was noted the conjunctivas appeared pale Fundi showed a few patches of old exudation and some arteriovenous nicking Trachea was thought to be deviated slightly to the left Several small non tender nodes were palpated in the right axillary region A bulge was noted at the base of the thorax posteriorly on the right There was flatness of the percussion note in the right axilla below the third rib and below the angle of the scapula There was suppression of breath sounds in these areas No rales were heard Vocal fremitus was normally transmitted The heart was not enlarged There was a soft blowing systolic murmur heard at the apex The abdominal wall was rather obese and the muscles were held rigidly Spleen and liver did not seem enlarged No tenderness was noted No abnormalities were described on pelvic examination

COURSE IN THE HOSPITAL The temperature ranged from 102 to 104 A thoracentesis was attempted but no fluid was obtained Pallor increased and the patient showed marked sweating Tenderness developed below the costal margin on the right with tenderness on heavy percussion over the liver which became palpable the edge extending 3 to 4 fingerbreadths below the costal margin Therapy was tried with sulfamerazine emetine and potassium iodide with no effects on the temperature No fluid or pus could be obtained from the sub-diaphragmatic space On March 11 abdominal exploration was performed and the patient died a few days later

LABORATORY DATA Blood serologic test for syphilis was positive Red blood cells numbered 2 9 million hemoglobin 8 5 gm hematocrit 26

icterus index 5 sedimentation rate 26 mm per hour leukocyte count on admission 7 700 with 1% juvenile neutrophils 73% segmented neutrophils 23% lymphocytes and 3% monocytes On smear the cells appeared hyper chromic and numerous target cells were seen Platelets appeared normal

Stool examinations were negative for blood and parasites Urine had a specific gravity of 1 014 with a trace of albumin There were 20–30 white blood cells per high power field and an occasional crenated red cell but no casts Culture of a voided specimen was sterile Blood cultures showed no growth in 7 days Sputum culture on February 12 showed moderate growth of Friedlander s bacillus and hemolytic *Staphylococcus albus* Agglutinations for tularemia and brucella were negative as were hetero phile agglutinations Tuberculin test PPD first strength was negative second strength was 1 plus

Blood chemical examinations on March 3 showed total serum protein 8 gm % albumin 3 63 gm % bilirubin less than 0 8 mg % serum non protein nitrogen 24 mg % phosphatase activity 4 6 units cephalin floccula tion positive 1 plus Bromsulfalein test of liver function showed 38% retention

X ray examinations on February 10 showed heart normal in size and configuration and aorta tortuous There was infiltration in the lower portion of the right lung field due to a pneumonic process Film of the abdomen on February 14 showed no evidence of gas or fluid between the diaphragm and the liver Fluoroscopic examination of the chest on the same day showed that the diaphragm on the right did move but did not have the excursions of that on the left The dense triangular area at the base was again noted

Discussion This case presents a very interesting problem in diagnosis with two important aspects (1) the difficulty of differen tiating at times between disease in the lower thorax and in the ab domen and (2) the differential diagnosis in cases of high fever of obscure origin

This 56-year old Negro female had an illness lasting about 8 weeks with high fever pleuritic chest pain loss of weight signs of fluid at the lung base although no fluid could be obtained on taps severe anemia progressive enlargement of the liver with tenderness impaired excretion of bromsulfalein and no leukocytosis or elevation of bilirubin

When she was first seen chest pain was prominent there were evident changes over the right lower lung field and the only abdom inal finding was some rigidity without tenderness One might postu late that the abdominal findings were secondary to involvement of the diaphragmatic portion of the pleura However later the liver was definitely enlarged and there was evidence of diffuse hepatic disease with two tests of bromsulfalein excretion showing a high degree of

retention of the dye The diagnosis therefore must explain involvement of the liver as well as the changes recorded above the diaphragm

The central feature about which it seems most logical to assemble the diagnostic possibilities is the continued high fever without leukocytosis

Blood cultures did not reveal evidence of a *bacteremia* Ordinarily with infections due to streptococci staphylococci or other pyogenic organisms, it is easy to obtain positive cultures With other organisms such as gonococcus or bacteroides, it is more difficult Vegetative endocarditis must always be considered in a patient with a heart murmur as was observed here However, although she had anemia, there were no other suggestive manifestations, and the localization of the changes in the liver and lower chest, and the negative blood cultures before chemotherapy seem to rule out this possibility

This patient might have had a pelvic abscess with metastatic lesions in the liver and chest There was no story of lower abdominal pain no leukocytosis and unless there was pylephlebitis one would not expect evidence of diffuse liver cell damage The story, the absence of sputum and the lack of rise in the leukocyte count are all against a pulmonary abscess It should be recalled that Friedländer s bacilli were found in the sputum This organism may cause a pneumonia followed by chronic abscess Hepatic abscesses have also been reported with this organism as the cause

Of the localized infections without abscess formation such as pyelitis meningitis or encephalitis there is no evidence except possibly of pyelitis with extension beyond the renal pelvis and involvement of the liver The urinary findings do not support this

There are four *specific infections* which may be considered in this case syphilis tuberculosis actinomycosis and amebiasis Syphilis of the liver and lung are rare and in late syphilis would not be expected to result in such a fulminating illness as this High fever without leukocytosis in a Negro patient always suggests tuberculosis This disease rarely involves the liver to such a degree as was present in this case and the type and location of the lung lesion would be unusual Actinomycosis may involve lung and abdominal cavity but usually is not so rapidly advancing as was this disease The combination of lower right lung and right upper quadrant findings suggests amebiasis However the therapeutic test with emetine was a failure there was no leukocytosis and no parasites were seen in the stool

This woman was a Negro, and had anemia and abdominal pain with enlargement of the liver Sickle cell anemia seems unlikely but

thromboses are not uncommon in this disease and the pulmonary manifestations might have been due to embolism There was no record of search for sickle cells The first severe episode at the age of this patient would be rare One rarely gets predominant involvement in the liver and lung in any type of lymphoma so that diagnosis seems very unlikely

The sixth group of diseases to be considered is a miscellaneous group caused by toxic agents and products of tissue death such as drug fevers pulmonary and myocardial infarction accumulation of blood in body cavities etc Only one thing needs to be mentioned and that is the possibility that the pulmonary lesion was the result of an embolus being a complication of and not a primary part of the disease picture

The final possibility is a malignant tumor When one recalls the main features of this case fever without leukocytosis anemia loss of weight absence of response to chemotherapy failure to get pus on pleural or subdiaphragmatic taps all favor a diagnosis of carcinoma with metastasis Three major possibilities as to primary site present themselves—lung pleura liver Except for the pleural pain pulmonary symptoms were inconspicuous Primary bronchial neoplasms are rare in Negro females If this were a primary tumor of either pleura or lung it would be unusual for metastatic lesions in the liver to give evidence of diffuse liver involvement as was the case here The evidence points to a primary carcinoma of the liver and there may be an underlying portal cirrhosis The lung changes are probably due either to metastases or to a pulmonary embolus

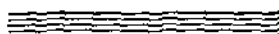
Anatomical Diagnosis (Autopsy No 18827) Cholelithiasis Scarring of gallbladder Dilatation bile ducts Adenocarcinoma of gallbladder growing into the liver and with metastasis in the liver Purulent bronchitis bronchial dilatation and bronchopneumonic foci both lower lobes atelectasis Acute splenic tumor and infarcts in spleen Thrombosis right iliac vein and first portion of vena cava Colloid adenoma thyroid

The middle lobe of the right lung showed purulent bronchiolitis and atelectasis The lower lobe was similarly collapsed and there was widespread purulent bronchitis together with lobular pneumonia in both lungs In the right lobe of the liver there was a large tumor mass probably largely necrotic The gallbladder was contracted its wall thickened and scarred and its lumen small It contained impacted stones and was surrounded by tumor The spleen was small and the cut surface showed several opaque areas suggesting little infarcts rather than metastases

Microscopically the gallbladder wall was scarred and in one place the section showed complete destruction of the wall by an adenocarcinoma which extended into the liver No metastases were found elsewhere There

was a fairly fresh thrombus with a purulent center in the vena cava There were old thrombi in branches of the hepatic vein

SUMMARY This 56 year old Negro female had an illness lasting 8 weeks with high fever loss of weight chest pain signs suggesting fluid at the right lung base severe anemia and progressive hepatomegaly with tenderness There was impaired excretion of bromsulfalein no elevation of serum bilirubin and no leukocytosis The case illustrates the difficulties of distinguishing between intrathoracic disease and a subdiaphragmatic lesion The causes of abscess and fever were reviewed and a final diagnosis of primary carcinoma of the liver was made Autopsy revealed a PRIMARY CARCINOMA OF THE GALLBLADDER with extension to the liver but also purulent bronchitis bronchial dilatation and bronchopneumonic foci in the lower lobes of both lungs



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Chapter 11

DISEASES INVOLVING THE LUNGS OR MEDIASTINUM

THE LUNGS may be involved in a wide variety of diseases Many difficult diagnostic problems originate with a history of hemoptysis or with the discovery of abnormal x ray shadows in the lung fields or mediastinum The headings under which these subjects will be considered here are chosen arbitrarily with view to dealing with the problems in the form in which they are most commonly encountered (1) inflammatory lesions of the lungs—so called pneumonitis (2) suppurative disease of the lungs with abscess formation (3) conditions which may be associated with hemoptysis and (4) mediastinal tumors

PNEUMONITIS

Pneumonitis or pneumonia may occur as a primary disease or it may be merely one of several manifestations of a generalized infection The identification of the causative organism does not necessarily determine whether one is dealing with a primary pneumonia Pneumococcal pneumonias are generally primary and the localization of the organisms in other areas is due to hematogenous metastases from the pulmonary infection In some other diseases for example typhus fever the involvement of the lungs occurs relatively late in the course of a generalized infection But in diseases such as tularemia and tuberculosis the pulmonary lesion may be either primary or secondary depending to at least some extent upon the portal of entry of the infecting organism It is not always possible to say whether the primary site of an infection is in the lungs but from the point of view of practical clinical diagnosis it is helpful to have in mind a classification of inflammatory lesions of the lungs such as is presented in Table 17 These lesions are in some instances discoverable

Table 17 Diseases Associated with Inflammatory Lesions in the Lungs (Pneumonitis)

I Diseases due to infectious agents
  A With the lungs as the principal site of disease
    1 Bacterial pneumonias due to
      a Pneumococcus
      b Beta hemolytic streptococcus
      c Staphylococcus
      d Friedlander s bacillus
      e *Pasteurella tularensis*
      f Tubercle bacillus
    2 Viral and rickettsial pneumonias
      a Primary atypical pneumonia
      b Influenza pneumonia
      c Ornithosis
      d Psittacosis
  B With involvement of the lungs as part of a generalized infection
    1 Bacterial
      a Tularemia
      b Typhoid fever
      c Brucellosis
      d Tuberculosis
      e Other enteric organisms
    2 Mycotic
      a Coccidioidomycosis
      b Histoplasmosis
      c Actinomycosis
      d Moniliasis
      e Cryptococcosis
    3 Viral
      a Smallpox
      b Chickenpox
      c Measles
      d Influenza
      e Lymphocytic choriomeningitis
      f Infectious mononucleosis
    4 Rickettsial
      a Typhus fevers
      b Q fever
    5 Unknown Agent
      a Sarcoidosis

II Pneumonitis associated with allergic states (anaphylactic pneumonia)
  A Post transfusion pneumonia
  B Serum disease pneumonia
  C Loffler s syndrome
  D Pneumonitis of rheumatic diseases
    1 Acute rheumatic fever
    2 Systemic lupus erythematosus

III Pneumonitis due to chemical and physical agents
  A Lipoid pneumonia
  B Inhalation of irritating gases (phosgene mustard)
  C Bagassosis
  D Byssinosis

IV Conditions which may be mistaken for pneumonitis
  A Carcinoma—primary or metastatic
  B Pulmonary infarction
  C Atelectasis due to plugging of bronchi
  D Pulmonary edema
  E. Idiopathic pulmonary siderosis

F Acute interstitial fibrosis
G Pulmonary adenomatosis
H Eosinophilic granulomatosis
I Silicosis
J Berylliosis
K Intrapulmonary hemorrhage

only by x ray examination In the cases in which they can be detected by physical examination their extent and certain morphological characteristics can be appreciated only by means of roentgenography It should always be remembered however that accurate radiological interpretation depends as much upon a knowledge of the clinical features of a disease as upon experience in differentiating the shadows seen in a film The shadows cast by areas of pneumonitis may be indistinguishable from those seen in pulmonary embolism interstitial pulmonary fibrosis chronic passive congestion or neoplastic disease The x ray is particularly helpful in determining whether certain symptoms are due to disease in the thorax or below the diaphragm Problems of this sort arise frequently particularly in children An acute pyelitis or a subdiaphragmatic abscess resulting from perforation of the appendix may produce respiratory pain and other symptoms suggesting pneumonia *Conversely* pneumonitis with pleurisy involving the outer portion of the diaphragm may produce pain which is referred to the abdomen simulating acute appendicitis In these situations a careful history a study of the pattern of the respiratory and abdominal movements and careful examination of the lungs and abdomen may give important leads but the final decision frequently depends upon roentgenography

The widespread use of antibiotics and chemotherapeutic agents in the treatment of all types of infections of the respiratory tract frequently modifies the course of pneumonia and makes interpretation difficult Treatment may have been started without the advice of a physician for what was assumed to be a simple respiratory infection When the patient is seen several days later the findings may be very bizarre In several cases recently encountered a widespread pleural friction rub was the only residual evidence of what had apparently been a suppressed bacterial pneumonia If the acute phase of the pneumonitis has been suppressed a sterile empyema or purulent pericarditis may develop and present a picture which is difficult to comprehend The situation may be further complicated by a drug allergy not infrequent in patients treated with sulfonamides or penicillin

Once it has been decided that the patient has pneumonitis one

should then make an effort to determine whether the pulmonary involvement is primary or part of a generalized disease Pneumococci account for a very large percentage of the cases of primary bacterial pneumonia As already mentioned the classic clinical picture of this disease is now frequently confused by inadequate antibiotic therapy Furthermore, after the diagnosis has been made and appropriate treatment started additional problems lie ahead For, although antibiotic therapy reduces the incidence of complications such as empyema pericarditis meningitis, endocarditis and arthritis, the recognition of these conditions may be rendered more difficult Pneumonia due to Friedlander s bacillus is particularly likely to occur in the poorly nourished alcoholic It may be suspected from the orange red color and gelatinous consistency of the sputum Bronchial plugging is frequent and may give rise to physical signs simulating those of pleural effusion There is a tendency for necrosis of the lung to occur This leads to cavity formation with a resulting chronic illness which may resemble tuberculosis Primary streptococcal pneumonitis is less common than the secondary variety, and the discovery of streptococcal pneumonia should lead one to search for some underlying disease

The successful use of antibiotics in the treatment of bacterial pneumonia has served to focus greater attention on the non bacterial types In many of these the causative agent has not been clearly identified It is probable that under the heading of primary atypical pneumonia many etiologic agents are involved The non bacterial pneumonias are usually not ushered in with a chill such as one sees in pneumococcal pneumonia and seldom is there rusty colored sputum pleurisy or leukocytosis In primary atypical pneumonia cough is an outstanding symptom substernal pain is common and there are fewer physical signs than one would expect from the x ray appearance of the lungs The onset may be gradual the respiratory rate may not be elevated and a relative bradycardia may be noted The leukocyte count low early in the disease occasionally rises to 15 000–20 000 in the second week A meningo encephalitis has been noted and when a high titer of cold agglutinins is present an acute hemolytic anemia may develop The pulmonary lesions are most dense in the hilar area Occasionally the pneumonitis may be migratory, but this feature is more characteristic of rheumatic pneumonia Influenzal pneumonia may have its onset with a grippe like syndrome with malaise and muscular aching but it may progress rapidly and lead to prostration and deep cyanosis Leukopenia is usually a striking

manifestation This type of infection may be difficult to interpret in non epidemic periods Ornithosis and psittacosis may produce a picture closely simulating that of primary atypical pneumonia The lead to the correct diagnosis usually comes from a history of contact with birds

A wide variety of diseases may exhibit pulmonary lesions at some stage in their progress In some of these for example in about one third of the cases of tularemic pneumonia the lesions in the lungs constitute the only evidence of visceral involvement and may therefore be confused with other types of primary bacterial pneumonia Characteristically the so called primary type of tularemic pneumonia has few physical signs In the x ray film it exhibits a patchy distribution and there is frequently an enlarged sentinel mediastinal lymph node which serves as a clue to the diagnosis Without this clue the diagnosis may be suggested by a history of contact with animal vectors chiefly wild rabbits but the vector varies with locality In some areas during the summer months the disease may be transmitted by deer flies and there may be no local lesion at the site of the fly bite Typhoid fever is now a rarity Hence pneumonitis which may accompany this disease is almost never encountered Pneumonitis may constitute the presenting manifestation of salmonella infections In adults this is usually observed as a complication of debilitating disease Chronic leukemia for example may be complicated by a *Salmonella choleraesuis* bacteremia and pneumonitis Tuberculous pneumonia should be suspected when the patient appears less ill than the extent of the pulmonary lesions would seem to warrant There is usually no accompanying leukocytosis Tubercle bacilli may not be found in the sputum until caseation begins some two or three weeks after the onset of the acute symptoms Pneumonitis in patients who have been in the San Joaquin Valley of California should immediately arouse suspicion of coccidioidomycosis This may simulate primary atypical pneumonia in the acute phase but may suggest neoplasm tuberculosis or other chronic type of infection in the progressive phase The presence of a thin walled cavity in the x ray films should arouse suspicion of coccidioidomycosis Unless sought with care these cavities may be easily overlooked

The pneumonitis associated with such obvious diseases as small pox chickenpox or measles rarely gives rise to any doubt about the causative agent However in such cases as well as in the pneumonitis associated with influenza it is important to make bacterial studies of the sputum to exclude secondary bacterial pneumonia

Such studies should include Gram and Ziehl Neelsen stains as well as cultures Frequently the secondary pneumonia is due to a hemo lytic streptococcal infection Pneumonia of this type is frequently accompanied by a copious thin pleural effusion There may be sup puration or organization of the pulmonary lesions Infection with staphylococci may lead to the development of multiple abscesses which go on to the formation of thin walled cavities

Typhus fever is an example of a rickettsial infection during the course of which pneumonitis may be prominent Like typhus, 'Q fever is essentially a systemic disease, but in many instances there is a prominent pneumonitis difficult to distinguish from primary atypical pneumonia except by isolation of the causative agent or by serologic tests There may be a history of contact with animal vectors

So called anaphylactic pneumonia may occur in the course of serum disease and in post transfusion reactions Loffler s syndrome is characterized by migratory rather dense areas of pneumonia in which eosinophils are prominent There may be an accompanying eosinophilia in the blood The pneumonitis of acute rheumatic fever is also characterized by its tendency to migrate It is usually accom panied by acute polyarthritis or other of the characteristic manifesta tions of the disease The pulmonary involvement in systemic lupus erythematosus may be a chronic process The x ray picture shows characteristic areas of platelike atelectasis and elevation of the dia phragm Although there are usually evidences of lupus in some of the other organs the pulmonary involvement is occasionally the out standing clinical manifestation of the disease

The inhalation of various chemical and physical agents may result in pneumonitis Lipoid pneumonia is particularly likely to be en countered in children who have aspirated substances containing fats or oils Pneumonitis due to the inhalation of irritating gases was common during World War I but is rarely encountered in civilian practice Bagassosis is due to the inhalation of a dust composed of sugar cane fibers Byssinosis is encountered in those who are exposed to heavy concentrations of cotton fiber dusts There are doubtless many types of dusts which may lead to pneumonitis With some dusts, for example those containing silicon and beryllium the char acteristic lesions are granulomatous and fibrotic rather than pneu monic

A number of the conditions which may be mistaken for pneumo nitis have been listed in Table 17 Although these should be borne con

stantly in mind it seems unnecessary to discuss all of them in detail at this point Some of them will be presented at greater length in the discussion of the illustrative cases Pulmonary infarction and atelectasis due to plugging of bronchi are particularly likely to be confused with acute pneumonia The acute interstitial fibrosis of Hamman and Rich may be distinguished by its patchy distribution relentless progress and the extreme degree of cyanosis and dyspnea Eosinophilic granulomas are usually accompanied by similar lesions elsewhere in the body biopsy of these lesions is the key to the diagnosis Idiopathic pulmonary siderosis is a rare disease in which multiple small pulmonary hemorrhages result in hemosiderin deposits and an inflammatory reaction simulating pneumonitis Large intrapulmonary hemorrhages may result in the development of relatively large areas simulating pneumonic consolidation Such areas may develop in the lower lobe when a hemorrhage has occurred from cavitation in the upper lobe Pulmonary adenomatosis is another rare condition which may be suspected when there is unusually copious production of sputum

Difficult diagnostic problems frequently arise when an area of pneumonitis fails to resolve after the acute phase of the illness has been passed This may occur in pneumococcal pneumonia Under these circumstances one should suspect a bronchial obstruction complicating tuberculosis or the development of a lung abscess In primary atypical pneumonia the infiltration may persist for two or three months and when it is localized in the upper lobe it may be difficult to distinguish from tuberculosis Lipoid pneumonia must be considered when the signs of pneumonitis become chronic One must consider also other unusual conditions such as the peculiar pneumonia associated with retinal cytoid bodies

In many types of pneumonitis pleural involvement gives rise to respiratory pain at an early stage sometimes before physical signs or x ray shadows are evident Pleurisy of sudden onset may also be encountered in other conditions such as pulmonary infarction tuberculous pleurisy lung abscesses carcinoma lymphoma rheumatic pleurisy and Bornholm disease (epidemic pleurodynia) In cases of recurrent pleurisy with or without effusion pulmonary embolism systemic lupus erythematosus and chronic pleurodynia should receive special consideration An exudate in the pleural cavity may be the result of extension of a pneumonitis but the infection may also have reached the pleura via the blood stream or the lymphatics or it may be due to primary pleural disease a bronchopleural fistula or exten

sion from infection below the diaphragm the mediastinum or one of the supporting structures of the thorax When an effusion is present examination of the fluid may yield crucial diagnostic information The fluid should be examined to determine whether it is a transudate or exudate Cell counts and bacterial stains should be made Concentrated fluid should be examined for tubercle bacilli Cultures should be grown under both aerobic and anaerobic conditions A cell block should be prepared for examination for malignant cells A bloody pleural effusion may result from previous tapping of the pleural cavity a fractured rib or other traumatic lesion malignant disease infarction leakage from an aneurysm, or other conditions

The distinction between pulmonary embolism and pneumonia may present particular problems The initial pain of pulmonary embolism may be intense It may be accompanied by a chill and followed by fever bloody expectoration and pulmonary signs indistinguishable from those of pneumonia This problem arises with greatest frequency in elderly individuals who have signs of pulmonary consolidation following a surgical operation The infarct may become infected with an organism such as the type I pneumococcus and an empyema due to this organism may develop and add to the confusion Embolism during the course of congestive heart failure frequently leads to pulmonary infarction and the appearance of clinical jaundice

Recurrent attacks of pneumonitis may present special diagnostic problems and should always arouse suspicion of some underlying disease such as bronchiectasis neoplasm or congenital cystic disease

PULMONARY SUPPURATION WITH ABSCESS FORMATION

The various causes of suppurative disease of the lung are listed in Table 18 The early recognition of pulmonary suppuration with the institution of adequate medical therapy is important if a long illness and a major surgical procedure are to be avoided In the acute stage an abscess may simulate pneumonia and no distinction may be possible by radiological techniques A history of alcoholic stupor, epilepsy surgical operation, or tooth extraction may suggest the causal factor Purulent and profuse sputum may soon appear The temperature course is usually remittent in type Acute lung abscess occurs more often on the right side and more frequently in the lower lobes, the sites of predilection being the dorsal segment of the lower lobe and the axillary segment of the upper with signs in the region of the 6th to 8th ribs posteriorly or high in the axilla The initial symp-

toms may be those of grippe but pain cough chills and sweats often appear early The clinical manifestations may begin several weeks after aspiration trauma or obstruction of a bronchus Careful examination of the sputum may disclose pus and elastic fibers Bacterial stains and a search for so called sulfur granules are also impor

Table 18 Pulmonary Suppurative Disease with Abscess Formation

I Simple abscess with mixed infection Acute chronic

II Specific infections
- A Tuberculosis
- B Friedlander s pneumonia
- C Actinomycosis
- D Amebiasis
- E Staphylococcal pneumonia
- F Coccidioidomycosis

III Resulting from bronchial obstruction
- A Bronchogenic carcinoma
- B Lymph node enlargement
  - 1 Tuberculosis
  - 2 Tumor
- C Aneurysm
- D Mediastinal tumors
- E Inspissated mucous plug with atelectasis

IV Due to foreign body
- A Aspiration during coma
  - 1 Anesthesia
  - 2 Epilepsy
  - 3 Alcoholism
- B After thoracic surgery or drainage of empyema
- C After penetrating wounds

V Complicating other diseases
- A Infected pulmonary infarction
- B Metastatic lesions during bacteremia (staphylococcal)
- C Congenital cystic disease of the lung
- D Bronchogenic cyst
- E Bronchiectasis

tant Hemoptysis is not uncommon and may be a serious complication

An abscess may be chronic without overt constitutional manifestations of infection In such circumstances neoplasm should be suspected Early diagnosis of this condition is essential for successful surgical treatment In fact in all conditions leading to pulmonary cavitation effective treatment either medical or surgical is dependent

sion from infection below the diaphragm the mediastinum or one of the supporting structures of the thorax When an effusion is present, examination of the fluid may yield crucial diagnostic information The fluid should be examined to determine whether it is a transudate or exudate Cell counts and bacterial stains should be made Concentrated fluid should be examined for tubercle bacilli Cultures should be grown under both aerobic and anaerobic conditions A cell block should be prepared for examination for malignant cells A bloody pleural effusion may result from previous tapping of the pleural cavity a fractured rib or other traumatic lesion malignant disease infarction leakage from an aneurysm, or other conditions

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nosis of mediastinal tumors The mediastinum is a particularly fertile ground for the development of tumors and cysts Anatomically it forms a septum between the lungs making them independent of each other as regards intrathoracic pressure It harbors important channels of communication such as the esophagus and the trachea and numerous important cardiovascular and nervous system components It is an important area of the lymphatic system containing the thoracic duct many lymph nodes and the thymus gland Thus it is a congested region whose boundary structures enclose a complex variety of epithelial muscular lymphatic vascular and nervous tissues which may serve as the locus for infections or give rise to tumors A tabulation of the principal types of mediastinal masses such as is shown in Table 20 has proved to be very useful in differential diagnosis This table was modified from one prepared by Berman Powell and Hennessee

The location of the mediastinal mass provides important evidence for diagnosis As a general rule esophageal tumors tumors of neurogenic origin and gastroenteric cysts occupy a posterior position Lymphoid tumors are commonly found in a central or antero central location whereas thymic tumors intrathoracic goiters metastatic malignant growths and teratomas usually occupy the anterior region The areas of the mediastinum may also be divided in planes When considered from this point of view thyroid tumors are located in the upper anterior compartment while pericardial cysts are found in the lower anterior compartment

Special diagnostic procedures may help in the differentiation of tumors in this area X ray films may be taken from various angles Fluoroscopy during a barium swallow is very useful Laminography may be used to obtain better radiographic definition Kymography and angiography are of particular assistance in distinguishing between solid tumors and aneurysms

The distinction between benign and malignant tumors usually cannot be made with accuracy except by exploratory thoracotomy but certain clinical points may be helpful Benign tumors usually grow slowly and are unaccompanied by constitutional symptoms Malignant tumors on the other hand may lead to a wide variety of complications such as pleural effusion obstruction of the superior vena cava or thoracic duct irritation or paralysis of nerves invasion of lung and metastases to peripleural and other lymph nodes Lymphoid tumors may be very sensitive to radiation while benign tumors and carcinomas seldom change in size when radiated When

Table 20 Tumors of the Mediastinum (Modified from Berman, Powell and Hennessee)

I Due to adenomas malignant disease or hyperplasia of
- A Thyroid
- B Parathyroids
- C Thymus
- D Nervous system
  - 1 Ganglioneuroma
  - 2 Neuroblastoma
  - 3 Neurofibroma
- E Connective tissue and fat
- F Bronchial tree
- G Esophagus
- H Heart including pericardium
- I Lymph nodes
  - 1 Leukemia
  - 2 Lymphoma
  - 3 Erythema nodosum

II Metastatic tumors

III Cystic tumors
- A Dermoids
- B Pericardial cysts
- C Bronchial cysts
- D Echinococcus cysts

IV Infections and granulomatous diseases
- A Of lymphatic structures
  - 1 Tuberculosis
  - 2 Sarcoid
  - 3 Other infections
- B Mediastinal abscess
  - 1 Secondary to perforation of esophagus or trachea
  - 2 From other sources
- C Empyema
- D Mediastinitis due to other causes

V Vascular lesions
- A Aneurysm of the aorta or other major vessels
- B Cardiac aneurysm

VI Other conditions which may simulate tumors of the mediastinum
- A Diaphragmatic hernia
- B Pulmonary cysts
- C Chest wall tumors
- D Thrombosis of the superior vena cava
- E Mediastinal collagenosis
- F Esophageal dilatation as in cardiospasm

clavicular lymph nodes are present they should be removed for biopsy prior to institution of radiotherapy or treatment with nitrogen mus tards Modern thoracic surgical technique makes exploratory thora cotomy a feasible diagnostic procedure in doubtful cases

Although not strictly a mediastinal tumor bronchogenic carcinoma is the most common intrathoracic neoplasm and it may be mistaken for a tumor arising in one of the mediastinal structures When it arises near the hilum the shadow in the roentgenogram is usually irregular at its peripheral border Precise diagnosis may be made by bronchoscopic biopsy or by finding groups of tumor cells in the bronchial secretion In almost every instance tumors arising in the superior sulcus are bronchogenic in origin Pain in the shoulder or arm may be present before clear cut changes can be seen in the x ray Horner s syndrome or nerve root involvement may occur Again when seen radiologically the border is usually irregular but differ entiation from a benign superior mediastinal tumor such as intra thoracic thyroid may be difficult Thoracotomy should be performed before one assumes that an inoperable malignant neoplasm is present An oat cell tumor is a more frequent invader of the mediastinum than is the squamous cell type of bronchogenic carcinoma

Aneurysms of the great vessels may also present difficult problems in diagnosis They may produce pain due to changes in the aortic wall or from pressure on neighboring structures Erosion of bones may lead to continuous and intense pain boring in character Pul monary compression may lead to atelectasis and secondary infection of the lung The latter may spread to the pleura causing pleural pain Esophageal pressure may give rise to dysphagia and pain on swallow ing Slow escape of blood into various structures may cause pain of increasing severity Fatal rupture may occur into the trachea esoph agus lung pericardium pleura or other structures The aneurysm may be small but so strategically located that serious dysfunction of the types described above appears early When the mediastinal mass shows expansile pulsation and the serologic test for syphilis is posi tive diagnosis may be easy but laminated clot frequently prevents pulsation and the diagnosis can be made only by contrast angiography or thoracotomy

With mediastinal abscess there is usually a history of foreign body in the esophagus ingestion of corrosive material instrumentation or trauma The constitutional evidences of an acute infection are promi nent However the development of an empyema of the mediastinum may go unnoticed during antibiotic therapy for pneumonia and may

present at a later time as a mediastinal mass with few manifestations of localized infection Tuberculosis and syphilis of the mediastinum may occur through extension of an infection of bone

Primary tumors of the mediastinum include those of neurogenic origin ganglioneuroma neuroblastoma, and neurofibroma As has been pointed out these neoplasms are almost always located posteriorly and are at times remarkably asymptomatic Dull pain often of segmental distribution may be the presenting complaint Evidence of bony erosion may be noted on radiological study The shadow of the tumor may be smooth and rounded or lobulated Dysfunction of the cervical sympathetics with Horner s syndrome is not infrequent Teratoid tumors which are the most common of the benign growths usually occupy the anterior mediastinum, grow very slowly, and may reach enormous size before symptoms are produced The commonest manifestations are persistent cough and dyspnea, less frequent are dysphagia hemoptysis or recurrent attacks of pneumonitis or asthmatic breathing The finding of bone or teeth in x ray films is important diagnostically Early surgery is indicated since about 15 per cent of these tumors become malignant Thymic tumors may be benign or malignant and are often cystic in nature In most instances those associated with myasthenia gravis are benign, but this is not always true Operation is advisable when such tumors are found by x ray or fluoroscopic examination Bronchogenic cysts and cysts of the pericardium are usually relatively asymptomatic unless they become infected Even though asymptomatic they should be explored by thoracotomy This is the only certain way of distinguishing them from the more serious types of tumors

Although many mediastinal tumors are almost entirely asymptomatic at the time of their discovery manifestations due to intrinsic dysfunction of the structure of origin and neighborhood signs produced by pressure may be discovered if carefully sought Root pain may suggest a tumor of neurogenic origin but it should be borne in mind that other neoplasms that press on the chest wall may irritate the intercostal nerves Lesions involving those spinal segments that innervate the heart may produce a syndrome difficult to distinguish from angina pectoris Horner s syndrome is more commonly seen with malignant tumors or syphilitic aneurysm and hoarseness may be due to involvement of the recurrent laryngeal nerve Respiratory symptoms are common and may provide evidence of bronchial compression Dysphagia may be indicative of esophageal obstruction either by external pressure or by carcinoma of the esophagus itself

Superior vena caval obstruction in the early stages before the classic findings are evident, may be detected by comparing the venous pressure in the arms with that in the legs If the obstruction is not due to primary venous thrombosis then it is usually indicative of a malignant tumor or an aortic aneurysm In the younger age group a tumor of lymphatic origin is the most likely In older individuals owing to recent changes in morbidity bronchogenic carcinoma is now a more common cause of vena caval obstruction than is syphilitic aneurysm Mediastinal collagenosis may give the appearance of a mediastinal tumor may result in the development of vena caval *obstruction and may lead to severe pulmonary hypertension from* involvement of the pulmonary venous system

Illustrative Cases

I

(#395829 Admitted August 18, 1946 Died August 23, 1946)

THIS 43 year old Negro laborer entered because of a 10-day illness characterized by fever and chills Four days before entry he had a shaking chill lasting for 15 minutes At this time he noted pain over the precordium accentuated by respiration He developed a cough productive of rusty colored sputum The next day sulfonamides were administered He lost his appetite and began to vomit Burning on urination developed and he had reddish urine for two days He stopped the drug and the urine became normal in color He worked in a saw mill and had had no infection preceding the present illness

PHYSICAL EXAMINATION on admission T 105 4 P 130 R 32 B P 170/110

The patient was disoriented the respirations were shallow and he had a cough productive of rosy tenacious sputum There was no lymph node enlargement The pupils reacted normally No cyanosis jaundice or pallor was noted The fundi were normal There was no cervical rigidity The trachea was in the midline The heart was normal The thorax expanded well but there was diminution in descent of the diaphragm There were palpable rhonchi at the left base A few medium rales were heard over both lung bases on inspiration and numerous sonorous rales over the entire chest There was tubular breathing just lateral to the left heart border The liver and spleen were not palpable The reflexes were hypoactive There were varicosities of both legs, but the legs were equal in size

COURSE IN THE HOSPITAL The patient lived only six days The temperature continued high in spite of penicillin and sulfamerazine administration The third day he became comatose His neck was stiff but spinal fluid examination revealed no abnormalities The signs of pulmonary consolidation became more extensive with tubular breathing whispered pectoriloquy and bronchophony over both lower lung fields On the day of death he developed oliguria The nonprotein nitrogen was 143 mg %

LABORATORY DATA Blood serologic test for syphilis was negative Urine showed 3 plus albumin white blood cells red blood cells and casts in small numbers Hemoglobin 15 gm hematocrit 44 sedimentation rate 34 mm per hour leukocyte counts were all normal except the second day when they numbered 15 000 with 86% polymorphonuclear cells Sickling

negative Sputum culture alpha streptococcus and *Staphylococcus aureus* A yeastlike organism was also grown Blood cultures were sterile No tubercle bacilli were found on either smear or culture Material obtained by lung puncture was sterile on culture Nonprotein nitrogen 38 mg / bilirubin 0 8 mg % chloride 94 mEq CO combining power 27 mEq Sulfonamide level 1 3 mg % Agglutination tests typhoid O and H para typhoid and cold negative On the 14th day of illness the agglutination test for *Pasteurella tularensis* was positive 1/160 Tuberculin skin test negative X ray of chest showed increased density in medial aspect of right base consistent with pneumonic consolidation Patchy irregular density was present in the second right anterior interspace and underlying the 3d rib Soft patchy irregular densities at the left lung base

DISCUSSION The duration of this illness was two weeks from onset to death It was characterized by a high sustained fever which did not respond to either penicillin or sulfonamide It seemed most likely to those who saw him that he had a virulent type of pneumonitis with bacteremia However it does not seem probable that this was one of the more common types of bacterial pneumonia Pneumococci could not be isolated the pneumonia was patchy and diffuse there was no response to chemotherapy and no bacteremia was found The Friedländer bacillus should have been found easily if it had been the cause Furthermore an overwhelming infection due to this organism is usually accompanied by blood stream invasion Staphylococcal pneumonia as a primary disease is not common When infection does begin in the lung blood stream invasion with the development of metastatic abscesses may occur late There might be no improvement with penicillin therapy since many staphylococci are penicillinase producers The cerebral manifestations could have been due to a brain abscess but this would be unusual in the absence of bacteremia

It was stated that a yeastlike organism was grown from the throat The identity of it was not reported It seems unlikely that any of the fungus infections which may involve the lung such as histoplasmosis coccidioidomycosis streptothricosis or other mycotic agents could have produced such a rapidly fatal infection

Primary atypical pneumonia due to a virus must be considered Although cerebral manifestations are occasionally seen the early onset of delirium leading to coma would be unusual The absence of cold agglutinins does not rule out this type of infection

Of the generalized infections which may be associated with pulmonic involvement typhoid fever is easily ruled out The pulse was always rapid there was never a leukopenia or splenic enlargement

and the agglutinations were negative at the end of the second week Rickettsial infections such as typhus fever and tick bite fever usually have a skin eruption during their course but the general picture of this illness makes it difficult to rule out these possibilities

Three further diseases remain which could explain this illness The first is tuberculous pneumonia and against this is the absence of involvement of the upper portions of the lung the failure to find tubercle bacilli and the negative tuberculin reaction Least impressive is the absence of bacilli In acute tuberculous pneumonia bacilli may not be present in the sputum until caseation develops some 10 to 14 days after onset None of these criteria is infallible but the three together militate against a diagnosis of tuberculosis Melioidosis due to *Malleomyces pseudomallei* can produce miliary granulomatous abscesses similar to those produced by *Malleomyces mallei* However, there are no pertinent facts to suggest these possibilities The typhoidal type of tularemia could explain most of the findings A history of definite exposure is often lacking In the presence of pulmonary involvement with no other local portal of entry there may be no discernible lymph node enlargement unless the disease lasts for a long period Rupture of one of the tubercle like lesions into the blood stream may result in rapid progress of the disease with coma and death The organisms are difficult to grow from the blood stream and may be missed on routine culture The single agglutination test, although not strongly positive, is suggestive as the agglutination reaction may not be fully developed until the third week

It seems quite possible that the final oliguria and uremia resulted from sulfonamide administration I do not believe that hypertension played any significant part in this acute illness

The final conclusion is that this patient died of tularemic pneumonia

ANATOMICAL DIAGNOSIS (Autopsy No 20111) Lobular pneumonia with necrosis and cavity formation both lungs, necroses in liver spleen bone marrow right adrenal and mediastinal lymph nodes (Tularemia) Hemoglobinuric nephrosis Thrush with ulceration of larynx Hyaline tubercles in hilar lymph nodes

The middle of the right lower lobe contained a ragged abscess cavity partly filled with necrotic material This was surrounded by a margin of yellowish firm tissue in which the pulmonary markings were not visible The remainder of the lobe showed almost confluent consolidation There was another much larger abscess in the posterior tip of the right middle lobe The hilar and tracheal lymph nodes were the seat of small abscess formation The spleen was enlarged

Microscopically the outlines of involved alveoli could be seen and these were filled with fibrin and leukocytes although the latter were scanty Further toward the periphery the alveoli were filled with coagulated fluid Scattered about the involved areas were vessels filled with thrombus material *There was no tubercle formation and the reaction to the infection was negligible* Necroses were found in the spleen and bone marrow and in a lymph node draining the lung Cords of liver cells as well as adrenal epithelium were necrotic and infiltrated with leukocytes No bacteria were stained in any of the tissues and in addition the culture of the lung at autopsy was sterile The anatomical changes were compatible with the diagnosis of tularemia and the lesions had the disposition seen in this disease The kidneys showed dilated tubules which contained red cells and hemoglobinuric material The change resembled that seen in transfusion reactions and burns and was probably related to the sulfonamide administration

SUMMARY This 43 year old Negro laborer entered because of a 10-day illness characterized by chills fever cough and a pleuritic type of pain in the chest Examination revealed fever disorientation pneumonitis and hypoactive reflexes On the 14th day of illness agglutination test for *Pasteurella tularensis* was positive 1/160 The pulmonary signs progressed and he became comatose there being no response to penicillin or sulfonamide After discussion of the various virulent infections associated with pulmonary signs tularemia seemed the best diagnosis particularly in view of the positive agglutination test Autopsy revealed lobular pneumonia with necrosis and cavity formation in both lungs due to TULAREMIA

II

(#117323 Admitted May 21, 1946 Died May 22 1946)

This 25 year old Negro woman complained of sudden onset of pain in her right chest For many years she had had vague joint pains On examination in 1938 the heart was not enlarged but a systolic apical murmur was noted and the pulmonic second sound was greater in intensity than the aortic

Two days before admission the patient developed a chest cold with cough and a feeling of weakness The day before she had a shaking chill and noted pain under her right breast which appeared after coughing She felt hot and developed generalized aching

Physical Examination on admission T 104, P 160 R 45 B P 70/50

The patient was critically ill There was no cyanosis or jaundice but the mucous membranes were pale She complained of pain of a pleural type over the right lower chest The retinal veins were tortuous The neck was supple the trachea was in the mid line The movements of the right chest were splinted There was dullness over both lung bases more on the right The breath sounds were blowing in character but only scattered rales were heard The heart was at the upper limit of normal in size The rate was rapid the rhythm regular and no murmurs were heard The veins of the neck were not *distended The liver and spleen were not enlarged* There was no edema and neurological examination was normal

Course in the Hospital Because it was thought she had pneumonia penicillin and sulfadiazine were given The pulse rate and temperature remained elevated Following a transfusion the blood pressure rose to 115/80 but 12 hours later was 70/50 There was evidence of spread of the *process to the left upper and right upper lobes Her dyspnea remained* severe but cyanosis was not noted The abdomen became distended Leucocyte count 2 200 on admission rose to 5 000 A thoracentesis was done and 125 ml of straw colored material removed No organisms were recovered from the fluid Twenty four hours after admission she became comatose and died

Laboratory Data *Blood serologic test for syphilis positive* hemoglobin 10 gm leukocyte count 2 200 with 76% juvenile neutrophils 21% segmented neutrophils no sickling Urine showed albumin 1 plus many epithelial cells occasional white and red blood cells no casts Variety of chemical examinations of blood all showed normal results except cholesterol 93 mg % Culture of nasopharynx showed heavy growth of type II *pneumococcus blood culture showed no growth*

DISCUSSION This was a fulminating disease which terminated fatally three days after onset There was severe dyspnea but inconspicuous cyanosis The clinical diagnosis was lobar pneumonia due to type II pneumococcus but there was no evidence of benefit from penicillin or sulfadiazine The blood pressure remained low the temperature and pulse rate high These facts and the absence of bacteremia in the face of such an overwhelming infection make this diagnosis unlikely in spite of the fact that type II pneumococcus is rarely found in the throat under other circumstances It would be unusual for a patient with pneumococcal pneumonia to die so early in the course of the disease The same objections hold for any of the other types of bacterial pneumonia such as those due to Friedlander s bacillus or the staphylococcus

Most of the non bacterial pneumonias would not be expected to produce such a fulminating disease even in the presence of anemia The clinical characteristics of a primary atypical pneumonia are those of an acute infection of gradual onset in which constitutional symptoms predominate over respiratory manifestations The disease is ordinarily of mild or moderate severity and dyspnea of this degree is unusual Of known types of non bacterial pneumonia there seems no reason to consider psittacosis ornithosis or Q fever An additional possibility is influenzal pneumonia but the lack of cyanosis is against this diagnosis

Although we have no specific evidence to eliminate tuberculosis it would not be expected to cause such a fulminating and rapidly fatal infection in a relatively healthy young woman

It seems reasonable to look for some other type of infection to explain this explosive disease picture Meningococcal infections may strike with dramatic suddenness and end fatally within even a few hours Purpuric phenomena are usually present and a marked bacteremia is found

This is not the clinical picture of acute interstitial fibrosis which develops over a longer period of time With this malady there is not only dyspnea but intense cyanosis with the picture of cor pulmonale before death

The history of joint pains is difficult to interpret This woman had certain of the constitutional features of sickle-cell disease such as tortuous retinal veins but in spite of a moderate anemia there were no grounds for making the diagnosis of sickle-cell anemia Symptoms such as joint pains may occur in patients with the sickle-cell trait who have no anemia In this case the vague pains plus the description of

the cardiac findings in 1938 raise the possibility that she had rheu matic fever with mitral valve disease

Assuming for a moment that this patient had chronic rheumatic fever with rheumatic valvulitis, could the fulminating terminal illness be explained on this basis? Pulmonary lesions occur in acute rheu matic fever and may spread with great rapidity However, frothy sputum and cyanosis are usually evident Dyspnea may be extreme, as it was in this case Leukocytosis is an almost invariable accom paniment of rheumatic pneumonia, and acute carditis also is usually evident There was leukopenia in this case but the heart was at the upper limits of normal size and the pulse rate was out of proportion to even such a high fever With a rate of 160 murmurs might not be audible The low blood pressure and pulse pressure are compatible with an acute myocarditis

Other possibilities may be mentioned for completeness but do not seem probable—for example, acute bacterial endocarditis involving the tricuspid or pulmonic valves and multiple pulmonary emboli from the heart or peripheral veins

The following diagnoses seem likely but the evidence to support them is not conclusive Rheumatic heart disease with mitral valve involvement acute rheumatic fever with acute myocarditis and pneu monitis sickle cell trait The leukopenia was striking and one has difficulty in dismissing the diagnosis of a viral type of pneumonitis If this were the situation (viral pneumonitis) then the positive blood serologic test for syphilis may be a biologic false positive There is certainly nothing to indicate that syphilis was concerned in the final illness

Anatomical Diagnosis (Autopsy No 19963) Bilateral virus pneu monia (influenza A) with widespread edema macrophages, hyaline membranes and areas of lobular polymorphonuclear consolidation (gram positive diplococci in stain) Mitral stenosis with marked scarring of mitral valve Dilatation and hypertrophy of left atrium Effusion pericardial pleural and peritoneal cavities Acute congestion liver Slight periportal scarring and chronic inflammation Hyalinized and calcified hilar lymph nodes History of sickle-cell anemia no splenic lesion

The lungs were heavy and full of edema coagulum The bronchi were reddened the nodes at the hilum and about the trachea were swollen In areas the lungs appeared dark in color and were firm No definite con solidation could be made out Influenza virus A was isolated in the chick embryo Grossly the condition of the lungs resembled extreme chronic passive congestion and the old mitral stenosis was consistent with this impression Microscopically however both lungs contained extensive lesions of virus pneumonia

SUMMARY This 25 year old Negro woman had a history suggestive of rheumatic fever and evidence of mitral valve disease Two days before admission she developed a chest cold and felt weak The following day she had a chill fever generalized aching and pain under the right breast after cough Examination revealed fever tachycardia hypotension dull ness over both lung bases and an occasional rale There was evidence of spread of the pneumonitis to the upper lobes The leukocyte count was 2 250 *Throat culture showed a type II pneumococcus In the presence of a* history of rheumatic fever and a fulminating illness with fever tachycardia and peculiar pulmonary signs a diagnosis of acute rheumatic fever with myocarditis and pneumonia was made However the leukopenia was an important clue and in view of the extreme dyspnea and rapid course more emphasis should have been placed on the possibility of a viral pneumonitis At autopsy mitral stenosis was found but the cause of the final illness was a VIRUS PNEUMONIA DUE TO INFLUENZA A

III

(#594873 Admitted January 9, 1952 Died January 10, 1952)

THIS 68 year old white woman was admitted in a semicomatose condition She had cared for her psychotic sister and during the preceding two years the sister had beaten her on occasions with resulting injuries to the head For six years the patient had been under treatment for high blood pressure and a failing heart Her chief complaint was dyspnea on exertion Three years before entry she developed headaches which had become worse during the past six months For eight months the ankles had been puffy On numerous occasions she complained of pain in the left shoulder and arm Five weeks before entry the sister was institutionalized and when the family visited the patient they found she had been ill for several days without adequate food After that she refused to lie down because of shortness of breath and was incontinent She had a severe non productive cough and complained of a lump in the throat and pressure under the manubrium Three weeks before admission she complained of fogginess of vision in the right eye For 10 days she had eaten poorly Two days before admission she was given exchange resins to relieve edema She became confused and on the morning of entry developed a rattle in her throat and thought she was dying On arrival in the accident department she was thought to have subsiding pulmonary edema The blood pressure was 100/60

PHYSICAL EXAMINATION on the ward T 97 P 70 R 12 B P 84/60

The patient was emaciated and appeared chronically and acutely ill She could be aroused only by painful stimuli Respirations were slow with shallow inspiration and prolonged expiration with audible rhonchi There was cyanosis The pupils were small (morphine) There was no lymphadenopathy The neck was resistant to forward movement The trachea was in the midline The neck veins were flat The thorax had an emphysematous appearance Over the right lung the percussion note was flat from the 6th rib to the base and the breath sounds were suppressed Breath sounds were harsh with prolonged expiration in other areas Coarse rhonchi were heard throughout, and near the angle of the scapula on the left medium moist rales were noted The heart was slightly enlarged and there were numerous extrasystoles The sounds were distant Loudest at the apex and transmitted toward the axilla was a high pitched cooing systolic murmur There was thickening of the peripheral arteries The liver edge extended

below the umbilicus There was edema of the legs and over the sacrum She moved all four extremities and the reflexes were hypoactive but equal

Course in the Hospital The patient s pulse rate and temperature gradually rose to normal levels the blood pressure to 110/80 The venous pressure was 130 mm (glucose) After a few hours she became more alert The peripheral pulses were palpable The right ulnar pulsation was stronger than the left and her right hand was warmer than the left The neck became supple but the moist rales persisted The cyanosis remained but improved when she was placed in oxygen Thoracentesis yielded 900 ml of pink fluid which clotted in 1 minute specific gravity was 1 010 red cell count was 95 000 and white cell count 2 000 with 78% polymorphonuclear cells A few hours later she was found dead in bed

Laboratory Data Blood serologic test for syphilis was negative Hemoglobin 12 5 gm hematocrit 39 icterus index 5 sedimentation rate 44 mm per hour Leukocyte count 55 000 (repeated in a few hours 35 500) with 8% juvenile neutrophils 86/ segmented neutrophils Urine specific gravity 1 020 albumin 2 plus occasional white cells and many crenated red cells but no casts culture showed *Staphylococcus albus* Blood non protein nitrogen was 48 mg / sugar 112 mg / cholesterol 222 mg / CO_2 combining power 28 4 mEq chloride 96 mEq sodium 137 mEq potassium 4 7 mEq alkaline phosphatase activity 7 6 units Culture of pleural fluid sterile

Electrocardiogram showed a rate of 83 P R interval 0 18 sec P waves normal left axis deviation slight sagging of the S T segment in leads 1 2 and V5 with inverted T waves

Discussion This patient had a history of illness extending over at least six years For approximately five weeks there was a change in the course of her illness the details of which are obscure but the dyspnea was more severe cough was pronounced and she com plained of substernal pain and became incontinent A few hours be fore admission she developed a rattle in her throat and was thought to have developed acute pulmonary edema There was fluid in the right pleural cavity the heart was enlarged and a systolic murmur was heard Hepatomegaly and edema were present but the venous pressure was not significantly elevated

She had had systemic hypertension for many years which prob ably accounted for cardiac insufficiency It would appear that there was no significant renal failure since the nonprotein nitrogen was only 48 mg% just before death The first question is whether the final illness was due to some complication of the hypertensive vascular disease Certainly the history and the findings are not typical of any of the common complications The vague story of substernal and shoulder pain might suggest coronary insufficiency the final episode

being coronary occlusion There was no history of pain associated with the final collapse the successive electrocardiograms showed no evidence of infarction, and a leukocytosis of this degree developing with such rapidity would be unexpected A dissecting aneurysm may have developed in view of the inequality of her pulses in the upper extremities, but such profound collapse without more severe pain would seem incompatible Leukocytosis may follow a pulmonary em bolus and the same holds for the blood tinged pleural effusion

Could she have had in addition to hypertension some other type of cardiac disease which contributed to the rapid progress of her ill ness in the few weeks before death? Certainly there was nothing to suggest congenital heart disease or pericardial involvement There was no evidence of primary pulmonary hypertension Her food intake was poor she had symptoms suggesting peripheral neuritis and a slow pulse a mitral murmur and edema, all compatible with beri beri That the enlarged liver was not due to heart failure alone is suggested by the only slightly elevated venous pressure The large hard liver and the low blood pressure could have been due to primary amyloidosis However the seemingly disproportional hepatomegaly may be more easily accounted for by fatty infiltration resulting from dietary deficiency

None of these suggested possibilities seems to furnish a clear ex planation of the entire course of events It would seem probable that the final illness was of several weeks rather than of several hours duration Perhaps the key feature requiring explanation is the ex treme leukocytosis with shift to the left The absence of a large spleen would seem to point against leukemia A severe internal hemorrhage is an unlikely cause as the hematocrit was 39 Reasons for suspecting malignant growth with extensive bone marrow metastasis do not exist Digitalis poisoning may be accompanied by leukocytosis but not of this degree Death of tissue resulting from infarction may give a high count but not of this magnitude unless very extensive There was no elevation of bilirubin to suggest a pulmonary infarct The only acute episode was a few hours before admission hardly allowing time for extensive necrosis of tissue to develop Occasionally tuber culosis will result in a leukemoid reaction The illness was possibly of five weeks duration with cough weight loss mental difficulties and an inflexible neck suggesting tuberculous meningitis but this type of blood picture would be more common in other types of bac terial infection such as

(1) Abscess formation (cerebral hepatic perirenal)
(2) Pneumococcal infection with pneumonia
(3) Meningitis
(4) Bacterial endocarditis

It is difficult to fit this puzzle together because the history was so vague The best possibility in view of the fulminating illness the leukocytosis and the cyanosis which cleared on administration of oxygen would be pneumonia Acute endocarditis could explain the anemia hematuria leukocytosis foggy vision and musical murmur

The low blood pressure and marked collapse with pulmonary edema could be associated with tubular degeneration of the adrenals

ANATOMICAL DIAGNOSIS (Autopsy No 23419) Generalized arteriosclerosis with narrowing of coronary and renal arteries and occlusion of left subclavian artery Calcified aortic valve History of hypertension and heart failure Right and left ventricular hypertrophy Generalized arteriolosclerosis Myocardial scarring Chronic passive congestion of the liver Pulmonary edema Acute lobar pneumonia left lung (gram positive diplococci) History of leukemoid reaction Tubular degeneration of the *adrenals Fibrinous pleuritis left lung Bilateral hydrothorax Emphysema* Medial cystic degeneration of medium sized pulmonary artery Atrophy cerebral cortex Pericardial scarring with hemosiderin deposits Cortical adenoma adrenal Focal necrosis adrenal cortex Acinar cell adenoma pancreas Carcinoid ileum Hyperplasia femoral marrow

The heart was markedly enlarged All leaflets of the aortic valve were thickened with calcified deposits and were rigid and stenosed There was a fresh fibrinous pleurisy over the posterior half of the left upper and lower lobes which were largely occupied by graying consolidation The left subclavian artery was occluded by arteriosclerotic plaques 1 cm from its orifice The thoracic and abdominal aorta were a calcified tube The orifices of both renal arteries were greatly reduced in size and cross section of the vessels distally showed marked narrowing Histologically the homogeneous fibrinopurulent exudate in the alveoli with excellent preservation of the alveolar walls and the absence of significant evidence of aspiration all suggest that this was a lobar pneumonia It was clearly more than a terminal pneumonia and had led to prominent tubular degeneration of the adrenal cortex Type III pneumococci were obtained at autopsy by lung puncture

SUMMARY This 68 year old white woman admitted in a semicomatose condition had hypertension and heart failure for six years For five weeks her diet was poor and dyspnea and edema had progressed For two days she was confused and developed a rattle in the throat Examination showed a subnormal temperature cyanosis dullness and suppression of breath sounds cardiomegaly extrasystoles a systolic murmur hepatomegaly and edema She improved on oxygen Nine hundred ml of fluid containing 2 000 white cells of which 78 per cent were polymorphonuclear

cells was removed from the right pleural cavity The white cell count was 55 000 with 8% juvenile neutrophils and 86% segmented neutrophils It seemed clear that the patient had had hypertension with chronic cardiac insufficiency The question was whether the final illness was a complication of this or some intercurrent disease The leukocytosis together with the pulmonary signs and the cyanosis which improved with oxygen suggested lobar pneumonia Autopsy showed coronary and renal arteriosclerosis, cardiac hypertrophy and chronic passive congestion There was a fresh LOBAR PNEUMONIA

IV

(#257708 Admitted April 21 1942 Died July 24 1942)

This 45 year old West Indian planter was admitted with a diagnosis of lung abscess and empyema He had had measles complicated by pneumonia at age 16 and in 1927 had sinusitis which necessitated irrigation

In April 1941 he developed fever with malaise and a diagnosis of influenza was made A few days later he had pain in the right chest continued to have fever and was told he had bronchopneumonia In June 1941 he was hospitalized because of continued fever A thoracentesis of the right chest was unsuccessful He developed violent attacks of coughing with purulent sputum On postural drainage his condition improved the temperature returning to normal A few days later fever returned and x rays revealed a cavity In January 1942 he had an hemoptysis and noticed easy fatigability and further fever His cough was productive of purulent and occasionally bloody sputum Administration of sulfathiazole and postural drainage gave little relief so he came to the United States for treatment

Physical Examination on admission T 99 4 P 108 R 28 B P 120/70

There was evidence of moderate loss of weight but no cyanosis pallor or clubbing The tongue was heavily coated and the pharynx slightly injected There was no lymphadenopathy The lower right lung border was at the 5th rib posteriorly and there was no movement with respiration The percussion note was dull as high as the 6th dorsal vertebra The *breath sounds in this area were suppressed and voice sounds and fremitus* were absent Occasional medium rales were heard The heart was normal The liver and spleen were not palpable The genitalia were normal Neurological examination showed no abnormalities

Laboratory Data Blood serologic test for syphilis negative Urinalysis blood chemical examinations hematological studies normal except for sedimentation rate of 21 mm per hour Sputum culture showed normal flora blood cultures were sterile No tubercle bacilli found on smear or culture stool examinations negative for blood and parasites X ray examination of the chest revealed thickening of the horizontal interlobar pleura on the right Fluoroscopic examination showed a loculated collection of fluid at the right base extending to the interlobar fissure and possibly into the fissure

On May 1 an exploratory operation was performed The right lung was bound down by dense adhesions After the right upper lobe was freed a hard mass of inflammatory tissue was found on the mediastinal surface of

the right lower lobe extending into the diaphragm Biopsy showed chronic inflammation and scarring of the lung

COURSE AFTER OPERATION During the postoperative period the patient was weak as well as dyspneic and cyanotic A collection of fluid in the right hemithorax was aspirated and was sterile A subcutaneous abscess developed near the right scapula and was incised with the release of purulent material cultures of which grew out a *Staphylococcus albus* The leukocyte count was 13 000 and the hemoglobin 11 8 gm The temperature spiked to 101 each day On May 29 x ray revealed fluid still present in the right thorax The thoracotomy incision was completely closed The patient perspired profusely and continued to cough with the production of bloody sputum He complained of pain in the region of the left shoulder On June 18 a bronchogram was done and none of the material reached the middle lobe Only the main bronchus to the right lower lobe was filled Bronchoscopic examination showed purulent material in each pyriform sinus The carina was widened as though a mass were pushing the right main stem bronchus upward The orifice of the right middle lobe bronchus was collapsed due to edema and the right lower lobe bronchus was filled with thick purulent exudate On July 4 edema was noted up to the knees and the hemoglobin had fallen to 10 5 gm At bronchoscopy three days later 30 ml of foul exudate containing a *Staphylococcus aureus* on culture was aspirated from the right lower lobe bronchus Further urine examinations showed albumin and occasional red cells and white cells with many granular casts The abdomen was distended and a fluid wave could be elicited A short systolic murmur was noted loudest in the 3rd interspace at the sternal border The blood pressure was 132/70 On July 6 a tender swelling was noted over the right elbow One week later 2 000 ml of serosanguinous pleural fluid was removed Smear for tubercle bacilli was negative The specific gravity was 1 016 with 4 plus albumin There were 37 500 cells 99% of which were red blood cells the remainder being lymphocytes Cultures were sterile The leukocyte count in the peripheral blood was 21 800 July 22 a subcutaneous swelling was noted in right interscapular area and 60 ml of foul smelling bloody fluid was aspirated The following day the patient became more dyspneic and cyanotic and the white count rose to 50 000 before death

DISCUSSION It would seem most logical to conclude that this patient had a suppurative process in the right lower lobe with abscess formation This may well have had its beginning with the pneumonitis complicating measles The exacerbations and remissions could have been associated with episodes of blockage of bronchi supplying the involved area followed by release of the accumulated purulent material The events following the operation may fit such a conception The impact of such a procedure in a person below his normal physical condition opened the way for a generalized infection, with bacteremia The metastatic processes in the elbow and interscapular area and the rapid progress to death followed It is quite con

ceivable that the patient also had an acute endocarditis and localized abscesses in other areas such as the brain may be found Such a conception seems logical but then the question arises whether there was some other underlying process in the lung

The possibilities other than that mentioned of a chronic pyogenic abscess following the post rubeola pneumonic infection are (1) amebiasis (2) mycotic infection (3) tuberculosis (4) neoplasm

Endameba histolytica may reach the lung either through the blood stream and produce an abscess or by extension of an abscess of the liver The latter is the more frequent course of events with the resulting development of an empyema If there is no secondary bacterial infection the exudate in the pleural cavity may be similar to that in the liver—so called anchovy sauce material However secondary infection is common and the hepatic involvement may be overlooked the empyema being considered bacterial in origin This patient was from a tropical area The process in the lung is in the right lower lobe and the involvement extends to the diaphragm There need be no clinical evidence of amebic colitis The sudden expectoration of pus is not uncommon as these lesions frequently rupture into a bronchus The type of pus brought up at first was not the typical material but amebic abscesses may develop insidiously and become secondarily infected before rupture occurs

In actinomycosis of the lung the early symptoms are those of a subacute pulmonary infection with cough fever and expectoration of mucopurulent sometimes bloody material Small abscesses form in the lung and frequently involve the pleura The findings in the early stages resemble those of tuberculosis As the disease progresses areas of consolidation develop with ill defined patches of rarefaction The pleura becomes adherent and pockets of fluid may form The ribs are infected and sinuses develop as the process burrows through the chest wall The acuteness of the onset and the failure of bilateral infection to develop until the end are against this possibility but the interscapular lesion may have represented direct extension of an actinomycotic infection from the lung No search was made for fungi and no cultures were made on suitable media These are the only ways in which such a diagnosis can be definitely established

Numerous attempts were made to find acid fast bacilli in sputum bronchial exudate and ascitic fluid without success The development of a purulent infection of this type particularly in the lower lobe would most likely be due to involvement of the bronchial wall by the tuberculous infection with resulting obstruction Of this there was

no evidence and tuberculous lesions were not found in the biopsy It is difficult to rule out this possibility although the clinical course of the illness is against it

The age of the patient and the duration of the illness are compatible with a diagnosis of pulmonary neoplasm with necrosis and suppuration Such a lesion could have been missed at the exploratory operation but it seems unlikely There were no definite findings to suggest metastatic lesions, and the rapidity of onset of symptoms, with development of an abscess would be unusual unless there was bronchial involvement with obstruction Neither the bronchograms nor bronchoscopic examinations revealed such a condition

The nature of the postulated bacteremia deserves further comment Anaerobic streptococci are usually present in putrid pulmonary lesions The distinguishing feature about this organism is its ability to cause necrosis with the production of a putrid odor If the primary focus is in the lung abscesses may develop in the distribution of the systemic circulation In the case described by Fisher and Abernethy, pulmonary gangrene with putrid empyema was followed by development of subcutaneous gas containing abscesses and metastatic suppuration of a clavicle and knee joint Staphylococcal bacteremia is characterized by metastatic abscesses, the kidneys being the most frequent site The more chronic cases may show subcutaneous lesions and acute endocarditis is more common than in streptococcal bacteremia A marked leukocytosis is the rule These two organisms could have been responsible for the widespread infection which this patient undoubtedly had

In a patient with a chronic infection who develops edema with ascites and changes in the urine the question of amyloid disease arises Usually there is more marked albuminuria than was present here Renal amyloidosis is generally part of a widespread process in which the liver and spleen are involved These organs were never palpable in this patient

From the mode of onset and the course of the illness it would seem most likely that this was a chronic pulmonary abscess complicated by a postoperative bacteremia Actinomycosis is difficult to rule out It might explain the involvement of the diaphragm the possible direct spread to the chest wall, and also the evidence of widespread infection terminally

ANATOMICAL DIAGNOSIS (Autopsy No 17963) Multiple lung abscesses (actinomycotic) right Dense fibrous pleural adhesions right Empyema right with rupture through diaphragm Subphrenic abscess

right Fibrous and fibrinopurulent pericarditis Purulent mediastinitis with extension to and abscess of left lobe of thyroid (actinomycotic) Thoracotomy right with draining sinuses Pleural effusion left with fibrinopurulent exudate Acute splenic tumor Chronic passive congestion Ascites Abscess right elbow

The lobes of the liver were adherent to the diaphragm There was a perforation in the right diaphragm connecting the pleural and abdominal cavities just to the right of the inferior vena cava The left pleural cavity contained 700 ml of thin hemorrhagic fluid In the few areas where the lung was free the visceral pleura was covered by a fibrinopurulent exudate The pericardial cavity contained a small amount of fibrinopurulent material The bronchi were injected and contained hemorrhagic purulent exudate In the right lower lobe on its lateral aspect there was an abscess cavity measuring 2 cm in diameter Examination of the microscopic sections showed numerous actinomycotic abscesses in the lung associated with dense scarring The section from the heart showed an extension from the infected lung and pleura into the pericardial sac There was dense infection and scarring over the right auricle at the entrance of the vena cava which provided a reason for the chronic passive congestion of the liver

SUMMARY This 45 year old West Indian one year before death developed evidence of a pulmonary abscess He had intermittent symptoms over the next few months No pathogenic organisms were demonstrated Exploratory thoracotomy revealed inflammatory tissue in the right lower lobe He continued to have fever and cough with bloody sputum Fluid reaccumulated in the right pleural cavity and edema ascites and urinary abnormalities developed Bronchoscopy revealed evidence of a mass displacing the bronchus upward It seemed clear that there was a suppurative process involving the right lower chest which appeared to spread systemically as well as locally The possibilities discussed were pyogenic abscess amebiasis tuberculosis neoplasm and actinomycosis The most likely diagnosis seemed to be chronic lung abscess but in view of the chronicity of the process and the nature of the operative findings actinomycosis could not be ruled out At autopsy there was ACTINOMYCOSIS with abscesses in the lung and extension to the pleura pericardium and peritoneal cavity

V

(#257875 Admitted May 1, 1942 Died May 8, 1942)

THIS 62 year old white male complained of cough dyspnea and weakness of two months duration His wife had died 18 years previously of tuberculosis

Two months before admission he developed a persistent cough which became productive of mucopurulent sputum On several occasions his sputum was blood tinged He developed anorexia and lost weight There was increasing dyspnea but no orthopnea or edema During the two weeks before entry he had attacks of stabbing pain in the left lower axilla associated with paroxysms of cough Hoarseness was present from the onset

PHYSICAL EXAMINATION on admission T 102 4 P 88 R 25 B P 85/50

The patient appeared chronically ill and had lost weight His face was flushed The fundi were normal The few remaining teeth were carious The neck was supple The trachea was in the midline There was a small movable lymph node in the left supraclavicular region but no general lymphadenopathy The anteroposterior diameter of the thorax was increased There was a massive left pleural effusion and occasional sibilant and sonorous rales were heard throughout the chest The heart sounds were distant and a pleuro pericardial friction rub was heard The abdomen was soft and the liver edge was palpated just below the costal margin The prostate was enlarged There was clubbing of the toes but not of the fingers

COURSE IN THE HOSPITAL Two liters of slightly cloudy straw colored pleural fluid was removed Following this the temperature rose to 103 6 and fever was intermittent until death On May 6 1200 ml of fluid was removed with no improvement in dyspnea The pleuro pericardial rub persisted and on May 7 pulmonary edema developed The venous pressure was 110 mm of saline Culture of the fluid from the second thoracentesis revealed type VII pneumococci so sulfadiazine was given The patient died on May 8

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin 11 gm sedimentation rate 32 mm per hour (corrected) Leukocyte count 10 900 with normal differential Urine normal except for occasional red and white blood cells Blood nonprotein nitrogen 32 mg % CO_2 combining power 65 vol % Total protein 5 gm % Vital capacity 1 3 liters Pleural fluid specific gravity 1 016 2400 white cells 57% polymorphonuclear cells 36% lymphocytes and 7% monocytes No

tubercle bacilli were seen in smears and the guinea pig inoculated did not die of tuberculosis No tumor cells were found in a section of spun sediment Sputum culture May 3 was negative for pneumococci May 7 there was a pure culture of type VII pneumococcus Blood culture May 7 type VII pneumococcus 250 colonies per ml X ray examination on May 1 showed dense clouding over the lower two thirds of the left lung field There was no shift of the mediastinum In the film taken after the first thoracentesis there were changes suggesting a parenchymal lesion in the left lower lobe

DISCUSSION The possible diagnoses in this case include bronchiectasis lung abscess pulmonary infarction aneurysm tuberculosis actinomycosis metastatic neoplasm and primary neoplasm of the lung or pleura It would be unusual in a case of bronchiectasis to have the first development of symptoms at this age One would have to assume that a bronchial obstruction had developed with abscess formation and infection of the pleura A simple pulmonary abscess with pleural involvement must be considered These lesions can develop with no known provocation The sputum is often bloody but is usually more abundant and has a disagreeable odor Pulmonary infection may develop around an abscess with resulting involvement of the pleura and the development of empyema The leukocyte count was essentially normal The character and the amount of sputum and the massive pleural effusion are strong points against pulmonary abscess Clubbing of the digits may appear early and progress rapidly but in this case it was noted in the toes and not the fingers so its significance is doubtful

No source in the heart or peripheral veins for a pulmonary embolus was demonstrated Massive pleural effusions secondary to infarction are usually bloody The fluid may become infected when secondary infection has taken place in the infarct There was no sudden onset here to suggest an embolus

Hoarseness brings up the possibility of an aneurysm which may lead to hemoptysis and pleural effusion The blood serologic test for syphilis was negative there was no tracheal tug and the pleural fluid contained no blood Dissecting aneurysm does not produce this type of picture and vascular disease seems a remote possibility

The remaining possibilities tuberculosis and neoplasm will be difficult to distinguish between Carcinoma of the lung may simulate any other pulmonary disease The early symptoms may be those of a mediastinal tumor including hoarseness When the lung is invaded by the tumor tuberculosis fungus infection and bronchopneumonia may be simulated When such complications as abscess formation

bronchiectasis, and empyema develop the underlying tumor may be easily overlooked Tuberculosis is one of the commonest chronic infections of the lung and may be active at any age It is more often confused with carcinoma than any other disease When an early manifestation of carcinoma is a pleural effusion the distinction between the two is particularly difficult In both diseases there may be fever, cough, sputum loss of weight and signs of fluid or consolidation Usually there is more fever and less pain in tuberculosis and the absence of rales favors carcinoma In advanced pulmonary tuberculosis careful search of the sputum will usually reveal bacilli The x ray film taken after removal of pleural fluid showed a lesion in the lower lobe which would favor carcinoma over tuberculosis

The age of the patient the location of the lesion in the lower lung field the nature of the effusion, with 57 per cent polymorphonuclear cells and the absence of tubercle bacilli in either pleural fluid or sputum all point to this being non tuberculous and leave neoplasm as the best possibility There was evidently a secondary infection of the lung due to a type VII pneumococcus with infection of the pleural fluid and bacteremia The symptoms were all pulmonary so with the solitary lesion and no evidence to indicate another source for a primary neoplasm carcinoma of the lung is the probable diagnosis It seems likely that there was invasion of the pericardium as well as the pleura in view of the character of the friction rub

ANATOMICAL DIAGNOSIS (Autopsy No 17853) Squamous cell carcinoma of bronchus Partial obstruction of bronchus Abscess cavity (left upper lobe) Extension of tumor into mediastinum pericardium and heart Organizing and fresh fibrinous pericarditis Lobar pneumonia (pneumococcus type VII) involving left upper and lower lobes Organizing and fresh serofibrinous pleurisy left

There were fibrous tags attached to the pericardium and a fresher organizing fibrinopurulent exudate The pleural surfaces of the left lung were covered by an organizing fibrinopurulent exudate Both lobes were completely consolidated In the anterior and inferior portion of the upper lobe there was a large abscess 6 cm in diameter A large bronchus opened directly into this and at the site of entrance there was narrowing due to a tumor The pericardium was adherent to the wall of the abscess On microscopic section the tumor proved to be a squamous cell carcinoma arising from the bronchus It extended all about the hilum of the lung and into the mediastinum as well as through the pericardium Extension into the left auricle and ventricle was noted

SUMMARY This 62 year old white male had a two months illness characterized by cough blood tinged sputum dyspnea pain in the left chest hoarseness and loss of weight He was febrile appeared chronically

ill and had a left pleural effusion and a pleuro pericardial friction rub A few days after admission he died with an overwhelming infection Tuberculosis or neoplasm seemed the most likely cause of the underlying pulmonary disease His age the location of the lesion the paucity of pulmonary signs the nature of the pleural effusion and the failure to find tubercle bacilli were points in favor of carcinoma of the lung A squamous cell CARCINOMA OF THE LUNG was found with bronchial obstruction abscess formation and extension into the mediastinum the pericardial cavity and the heart

VI

(#494060 Admitted September 7, 1949
Died September 16, 1949)

THIS 63 year old white laborer complained of dyspnea and weakness of one month s duration His father and brother both died of carcinoma of the stomach

In September 1946 he developed a severe pain in the right sacroiliac region aggravated by weight bearing sneezing and coughing He continued to have low back pain after the acute attack subsided In May 1949 a diagnosis of right sacroiliac arthritis was made He complained of loss of weight and a mass was seen in the chest x ray in the region of the arch of the aorta He had pectus excavatum however and it was thought that the resulting distortion of the chest might result in such an abnormal shadow

One month before admission he developed dyspnea and weakness which progressed in severity He had cough productive of small amounts of whitish sputum and swelling of the ankles but no orthopnea A few days prior to admission he noticed pain in the left lower chest on inspiration There was also discomfort beneath the sternum and in the epigastrium For a period of several weeks he had complained of substernal burning unrelated to exertion

PHYSICAL EXAMINATION on admission T 102 P 104 R 20 BP 100/60

The patient had lost weight his breathing was Cheyne Stokes in type and there was inability to pay attention Lumbar kyphosis was present and tenderness was noted on pressure over the right sacroiliac joint There was no lymphadenopathy The pupils reacted normally The neck veins were not distended There was a questionable tracheal tug thought to be transmitted The anteroposterior diameter of the chest was increased and pectus excavatum was noted No dullness was noted on percussion over the lungs The breath sounds were loud and bronchial on the left posteriorly There was an increase in retromanubrial dullness to the left in the 2nd interspace The heart was not enlarged and no murmurs were heard The liver and spleen were not palpated The genitalia were normal and the prostate small The deep tendon reflexes were sluggish but equal In the lumbosacral region there was a firm irregular subcutaneous mass

COURSE IN THE HOSPITAL Temperature ranged between 100 and 103 His clouded mental state grew worse The cough and pain in his chest subsided He did not become strong enough to make bronchoscopy feasible Nine days after admission he was found dead in bed

LABORATORY DATA Blood serologic test for syphilis negative Hemoglobin 11 5 gm Leukocyte count 10 000 to 13 000 with 3/ myelocytes 3% juvenile neutrophils and 85% segmented neutrophils Sedimentation rate 30 mm per hour (corrected) Urine specific gravity 1 020 trace of albumin Throat cultures beta hemolytic streptococci and unclassified pneumococci Sputum negative for tubercle bacilli Tuberculin test first strength PPD negative Blood nonprotein nitrogen 30 mg % fasting blood sugar 104 mg % calcium 9 6 mg % phosphorus 4 mg / CO_2-combining power 27 6 mEq chloride 91 mEq Total serum protein 4 6 gm / with 2 9 gm % albumin Alkaline phosphatase activity 10 Bodansky units Chest x ray in May 1949 showed the heart was normal A mass about the size of a lemon merged with the left border of the aortic arch This was not expansile but did transmit the pulsation of the aorta The bronchovascular pattern was increased Both pleural caps were thickened There was an arrested type of tuberculosis in the left apical area Pectus excavatum was present with shift of the mediastinum to the left The esophagus appeared normal on barium swallow X ray on September 7 1949 showed a lobulated mass measuring approximately 7 by 9 cm in the left upper mediastinum in the region of the aortic arch partially obscuring the aortic knob and the upper aspect of the left cardiac border Extending from this area linear strands of increased density were seen directed toward the left apical region Small patchy areas of mottled infiltration were noted in the upper third of the left lung field The remainder of the lung was emphysematous The heart appeared to be shifted to the left On September 14 1949 there had been a definite increase in the process involving the left upper lung field The mottled infiltration extended as far as the 11th rib posteriorly

DISCUSSION There are a number of well documented facts about this patient s illness which must be encompassed by a single diagnosis if possible It might seem unlikely that the back pain which brought him to the hospital had any relation to the intrathoracic changes which led to the dyspnea but the two may well be due to the same disease

The fact that the tumor grew in size over a period of a few weeks and occupied a region adjacent to the arch of the aorta is important The location of the mass and the course of the illness are against a thyroid or parathyroid tumor Neoplasms of nervous tissue almost uniformly originate in the posterior mediastinum The esophagus appeared normal on barium swallow There was no evidence that the tumor was cystic and none of the cystic tumors would explain the pulmonary manifestations The location of the mass the absence of intrinsic pulsation the lack of any pressure signs in the presence of evident increase in size and the negative blood serologic test for syphilis all militate against the diagnosis of aortic aneurysm

From review of the x ray films, the lung lesion is not believed to be due to atelectasis There was parenchymal involvement which how ever, did not produce significant physical signs such as one would expect from a pyogenic infection The most likely possibilities are (1) malignant teratoma (2) tuberculosis or actinomycosis, (3) bron chogenic carcinoma, (4) carcinoma of the thymus, (5) lymphosar coma

In a man of this age it would be unusual for a teratoma to become malignant The appearance of the pulmonary abnormality is com patible with tuberculosis and the degree of fever favors infection However such a rapidly progressive tuberculous lesion should pro duce more physical signs After such a time interval tubercle bacilli should have been found and the tuberculin test should have been positive Also against this diagnosis is the extensive anterior medias tinal involvement as indicated by the increase in retromanubrial dull ness and the degree of change in size of the mediastinal mass This would be an unusual course for tuberculosis in a white man at age 63, as it would necessarily indicate massive lymph node involvement Actinomycosis is mentioned on y because it may produce an appear ance such as that seen in the x ray and may closely simulate tuber culosis

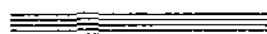
To differentiate between carcinoma of the lung carcinoma of the thymus and lymphosarcoma is difficult Carcinoma of the thymus is rare In x ray films it may present a lobulated appearance with a smooth edge as this tumor did and it may invade the lung Car cinoma of the lung rarely fills the anterior mediastinum as did this mass and usually has an irregular edge on x ray study Lymphosar coma on the other hand may originate in the thymus may thus fill the anterior mediastinum and may involve the lung by lymphatic spread without producing many physical signs The back pain might have been due to bone involvement occurring with either carcinoma of the lung or lymphosarcoma In a man of this age carcinoma seems the more likely possibility

ANATOMICAL DIAGNOSIS (Autopsy No 22005) Undifferentiated car cinoma in anterior mediastinum with extension to mediastinal lymph nodes and invasion and obstruction of left pulmonary artery and vein Organizing pneumonia of left lung with hemorrhages and areas of putrefac tion necrosis and excavation Terminal acute lobular pneumonia Acute splenic tumor Infection granules in cells of liver and adrenal cortex Peculiar subcutaneous calcified nodule over sacrum Eosinophilic hyper plasia of the bone marrow

Just above the left main bronchus and anteriorly there was a huge tumor

mass apparently in anthracotic lymphoid tissue which measured 10 cm in its greatest diameter There was no suggestion as to the site of origin Cross sections of both major bronchi showed tumor tissue invading their walls in a few places The right lung in all areas showed marked emphysema and scarring particularly prominent at the apex Even on microscopic examination the origin of the tumor was not certain It involved the mediastinal lymph nodes and extended around the vessels at the hilum of the left upper lobe The left main pulmonary artery was invaded by a tumor mass which filled its lumen No tumor could be identified in the lung itself A thymus could not be identified but there was a large mass of tumor lying anterior to the pericardium in the position of the thymus The histological appearance of the tumor was clearly epithelial but undifferentiated The pneumonia was undergoing organization and there were numerous small cavities due to necrosis of the tissue

SUMMARY This 63 year-old white man was found four months before death to have lost weight and to have a questionable mediastinal mass on x ray Later he developed dyspnea a productive cough and pleuritic pain On examination he had fever weight loss bronchial breathing over the left lung posteriorly and increase in retromanubrial dullness to the left His critical condition at the time of admission limited the extent of the special examinations X ray showed a lobulated mass in the region of the aortic arch The rapid increase in size of the tumor with progressive involvement of the lung but without physical signs suggested tumor rather than infection Carcinoma of the lung or thymus or a lymphosarcoma seemed the best possibilities It proved to be an undifferentiated CARCINOMA IN THE ANTERIOR MEDIASTINUM with extension to the mediastinal nodes and with invasion and obstruction of the left pulmonary artery and vein



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Chapter 12

MENINGITIS

THE DETECTION of signs of meningitis is relatively simple if a careful physical examination is performed. However, the diseases which may produce a primary infection of the meninges or a sterile meningeal reaction are numerous. Complex problems in making an etiological diagnosis often arise. Four major conditions which have in common a complaint of severe headache and/or the presence of resistance to anterior flexion of the neck may be mistaken for meningitis: (1) retropharyngeal abscess, particularly in children; (2) superior longitudinal sinus thrombosis; (3) subarachnoid hemorrhage; and (4) the meningismus which may accompany certain infections as, for example, typhoid fever. Pleocytosis and an increase in spinal fluid protein is rarely encountered in the early phase of any of these conditions, but an increase in spinal fluid protein is a common sequel of subarachnoid hemorrhage and longitudinal sinus thrombosis.

The various pathogenic bacteria listed in Table 21 may produce meningitis by the hematogenous route, by direct invasion of the meninges *through compound fractures or from focal infections such as* those of the ears or paranasal sinuses, or by introduction with spinal puncture. It is important to search carefully for any source of sepsis in or contiguous to the cranial cavity or vertebral column. When the *meningeal involvement is by spread from a neighboring infection* there may be an associated thrombosis of an intracranial venous sinus. The detection of other manifestations in a case of meningitis such as aural discharge, impairment of hearing, bony tenderness, signs of venous thrombosis, disturbance in vestibular function, cranial nerve dysfunction, exophthalmos, and visual field defects may provide the clue to its origin. Blood cultures should be routinely made and radiological examination of the sinuses and mastoids obtained when indicated. With ethmoiditis there may be oculomotor

Table 21 Causes of Meningitis

- I Bacterial infections
  - A Pyogenic infections due to
    - 1 Meningococci
    - 2 Influenza bacillus
    - 3 Pneumococci
    - 4 Streptococci
    - 5 *B pyocyaneus*
    - 6 Pasteurella tularensis
    - 7 Brucella
    - 8 Gonococci
    - 9 A aerogenes
    - 10 Salmonella
    - 11 Others
  - B Tuberculous infections
- II Spirochetal meningitis
  - A Syphilis
  - B Leptospirosis
- III Fungus infections
  - A Cryptococcus (torula)
  - B Aspergillus
  - C Coccidioidomycosis
  - D Actinomycosis
- IV Viral infections
  - A Benign lymphocytic choriomeningitis
  - B Epidemic parotitis
  - C Poliomyelitis
  - D Acute encephalitis
  - E Lymphopathia
  - F Measles
  - G Infectious hepatitis
  - H Infectious mononucleosis
  - I Herpes simplex and zoster
  - J Type C virus
- V Aseptic or sterile meningitis
  - A With mastoiditis or middle ear infection—otitic meningitis
  - B With brain abscess
  - C With mycotic aneurysm associated with bacterial endocarditis
  - D With brain tumor
    - 1 Primary
      - a Direct invasion of tumor cells
      - b Secondary to necrosis in tumor
    - 2 Metastatic
  - E With other intracranial vascular lesions (subdural hematoma embolism thrombosis)
  - F With systemic lupus erythematosus
  - G After intrathecal injections
  - H After lumbar puncture

dysfunction or retrobulbar neuritis without obvious clinical evidence of meningitis The spinal fluid in these cases should be examined routinely In pneumococcal meningitis without evidences of ear or sinus infection evidence of an acute endocarditis should be carefully searched for Meningitis secondary to frontal sinusitis is usually accompanied by a subdural or brain abscess Sudden onset of convulsions and motor impairment may result from thrombosis of the superior longitudinal sinus With a hemolytic streptococcal bacteremia the meningitis is nearly always associated with thrombosis of the lateral sinus or jugular bulb A predominance of polymorphonuclear cells in the spinal fluid may occur in certain forms of non bacterial meningitis Cultures of spinal fluid should be made and smears with Gram and methylene blue staining should be examined

Tuberculous meningitis is more common in children than in adults The organisms are usually difficult to find on direct examination of the spinal fluid and differentiation from other diseases causing a mononuclear pleocytosis may be a real problem In a significant number of cases of proved tuberculous meningitis there is a predominance of polymorphonuclear cells particularly in the early stages This fact combined with the acute onset which may take place after trauma to the head has led in certain instances to the mistaken diagnosis of a pyogenic meningitis Helpful points in the diagnosis of meningeal tuberculosis are (1) its frequent association with tuberculosis elsewhere (2) the almost invariably positive cutaneous tuberculin reaction and (3) the low spinal fluid chloride lower than in other diseases causing a mononuclear cell reaction

The clinical picture in syphilitic meningitis is usually one of three types (1) basilar involvement with multiple cranial nerve palsies (2) vertex involvement with symptoms such as convulsions motor paralysis and aphasia or (3) evidence of increased intracranial pressure making distinction from brain tumor or abscess difficult In other types of meningitis including tuberculous meningococcal and lymphocytic choriomeningitis there may be a false positive spinal fluid Wassermann reaction if the patient s blood serologic test for syphilis is positive Patients with asymptomatic neurosyphilis may develop any other type of meningitis so that a positive spinal fluid serologic test must be weighed carefully with the other evidence at hand In most cases of syphilitic meningitis the constitutional reaction indicative of infection is milder than is usually seen in tuberculosis

Rarely Weil s disease may be associated with meningitis that is clinically indistinguishable from benign lymphocytic choriomenin

gitis except by proper immunologic studies which should always be carried out in such cases

The most common type of fungus meningitis is that due to the Cryptococcus (torula) This organism has a predilection for the brain and meninges and the infection may slowly progress over many months with a low grade fever These small organisms which have no mycelia may be mistaken for lymphocytes in the spinal fluid In any case of mononuclear cell meningitis in which the etiologic agent has not been positively identified the cells should be examined after preparation with India ink and the fluid should be cultured on Sabaraud s medium In chronic meningitis due for example to torula infection or to tuberculosis intracranial hypertension may develop with resulting clinical manifestations simulating a third ventricle tumor Serous meningitis associated with middle ear infection may do the same Sometimes pneumographic studies are necessary to make a final differentiation

A variety of neurotropic viruses may produce the picture of so called aseptic meningitis Along the Eastern seaboard epidemic paro titis (mumps) meningitis accounts for about 20 per cent of the cases and benign lymphocytic choriomeningitis for 5 to 10 per cent A wide variety of agents including measles varicella herpes simplex and zoster lymphopathia infectious mononucleosis, and infectious hepatitis accounts for the remainder The diagnosis in these cases must be made on the basis of associated findings and specific im munological tests

In cases of brain abscess the degree of encapsulation of the local lesion determines to a large extent the type of changes encountered in the spinal fluid During the early phases there may be a marked pleocytosis predominantly polymorphonuclear The protein is often significantly elevated but if the fluid is sterile the glucose and chlo ride content will usually be normal As encapsulation of the abscess progresses the cell count diminishes and mononuclear cells predom inate

Occasionally one sees a meningeal reaction as the presenting fea ture in bacterial endocarditis The fever heart murmur anemia and other associated findings should lead one to the correct diagnosis

Tumor meningitis or so called sarcomatosis of the leptomeninges is rare It usually simulates a chronic type of meningitis It may occur in association with a primary cerebral neoplasm but more often complicates metastatic tumor or lymphoma involving the nerv ous system The cells seen are usually tumor cells mistaken for spinal

fluid lymphocytes However if necrotic tumor tissue impinges on the subarachnoid space or ventricular system a polymorphonuclear cell reaction may result In such cases as well as in those associated with the direct invasion of tumor cells the spinal fluid glucose may be depressed to the same degree as in bacterial infection and the chloride concentration may also be low

In several instances a marked meningeal reaction has been observed in patients with active systemic lupus erythematosus In one instance the patient had cervical rigidity and other clinical signs of meningeal irritation The cells in the spinal fluid may be significantly increased with a predominance of polymorphonuclear cells and in one case the spinal fluid protein reached 900 mg %

The injection of immune sera or other therapeutic agents into the subarachnoid space may give rise to a sterile meningitis accompanied by severe headache and cervical rigidity The cells in the cerebrospinal fluid may rise to such a level that the fluid becomes frankly cloudy At times it may be difficult to tell whether the meningeal reaction is due to progress of the original disease or to the therapeutic agent Simple lumbar puncture without injection of specific agents may occasionally give rise to a sterile meningitis This is usually mild It must be distinguished from the true bacterial meningitis which in rare instances follows lumbar puncture

Illustrative Cases

I

(#36660 Admitted April 19, 1931 Died May 1, 1931)

THIS 57 year old white mechanic complained of frontal headache nausea and vomiting and attacks of irrationality

One year before admission he received a blow on the left parietal region followed by swelling which subsided after a few days There was no period of unconsciousness but afterward he complained of frequent attacks of severe steady supraorbital headache Eight months before entry he received another blow this time on the left side of his face resulting in the loss of most of his teeth Again there was no period of unconsciousness After this he acted queerly at times and was forgetful particularly of recent events He had mood swings being exuberant at one time and depressed at another His behavior was described as vague and he had frequent nightmares

Eight weeks before admission he quit work because of more severe frontal headaches and during the next four weeks had frequent periods of vomiting without preceding nausea Four days before he entered the hospital incapacitating headaches and vomiting developed He became unruly and manic at night but was submissive by day although disoriented Just before admission he became apathetic and ceased eating

PHYSICAL EXAMINATION on admission T 100 P 70 R 20 BP 148/82

The patient was lying curled up, unwilling to be touched and complaining of feeling cold He was disoriented as to time and place It was difficult for him to finish a sentence the words becoming a jumble of sounds. The feet and hands were cool and bluish There was no generalized lymph node enlargement Extraocular movements were full and the pupillary reactions normal There was some blurring of the nasal side of the right disc The lungs were normal There was a systolic bruit heard at the base of the heart The liver and spleen were not palpable The prostate was enlarged The lower abdominal reflexes were absent Neurological examination was otherwise normal except for slight resistance of the neck to flexion

COURSE IN THE HOSPITAL During the first week the temperature ranged from 99 to 100 The pulse rate paralleled the temperature His orientation improved but on occasions he did not respond to questions

The neurosurgical consultant thought that he might have a subdural hematoma and advised ventriculography There was a bilateral hydrocephalus but no displacement of the ventricles An exploratory operation was done because a block in the region of the aqueduct was suspected The cisterna was large and there were fibrinous flakes at the upper part which were shelled off and sent for microscopic examination No evidence of tumor was found at operation The neck remained stiff a bilateral Kernig s sign developed and the deep reflexes became hyperactive He died seven days after operation

LABORATORY DATA Blood serologic test for syphilis was negative There was no anemia Leukocyte count was 10 120 with 88% polymorphonuclear cells Urine was normal Blood nonprotein nitrogen was 38 mg % Lumbar puncture April 20 initial pressure 280 mm of water dynamics *normal fluid faintly yellow cell count 278 lymphocytes 200 mg % protein* sugar 35 mg % Wassermann reaction negative colloidal mastic 0000000000 culture showed no growth Blood glucose taken at time of lumbar puncture 100 mg % X ray of skull normal

DISCUSSION The basic objective findings in this case were the sterile meningitis with the predominant lymphocytic pleocytosis It would seem probable that the correct diagnosis could be reached if one listed the various illnesses of this type which might be caused by trauma to the head

A history of some type of trauma to the head can be elicited in a large number of patients suffering from central nervous system disease Although direct injury to the brain may result or a disease such *as tuberculous meningitis may be precipitated the story of trauma is* often of no significance This man had within the year before death received two blows to the face or head neither of which resulted in unconsciousness the last being approximately eight months before admission A hemorrhagic pachymeningitis would not be expected to produce these spinal fluid findings A subdural hematoma should have given some displacement of the ventricles and would not produce a block at the aqueduct with enlargement of both lateral ventricles

The peculiar personality change in the year before death suggests the possibility of cerebral tumor originating in the frontal region Extension of such a tumor to involve the meninges could produce a sterile meningitis Again one would expect displacement of the ventricles The findings on ventriculography and at operation were not those of a supratentorial tumor

It seems most likely that this patient had some type of inflammatory disease involving the meninges about the base of the brain with at least partial blockage at the aqueduct From the nature of the cellular reaction in the spinal fluid the length of the illness and the

lack of growth on the routine cultures, a simple bacterial meningitis seems unlikely The length of the illness and the fatal outcome as well as the character of the fluid and the partial block are not compatible with the diagnosis of benign lymphocytic choriomeningitis

The three remaining possibilities are syphilis tuberculosis, and torulosis Syphilitic meningitis is usually more acute and, unless there is concomitant involvement of the nervous system as well would not produce personality changes over a period of months The pupillary reactions were normal and both blood and spinal fluid serological tests for syphilis were negative No cultures or stains were made for either fungi or tubercle bacilli No tuberculin tests were done, nor was an x ray of the chest taken It seems clear that the patient had not been entirely well for almost a year The personality changes and the slowly progressive illness with minimal signs of active infection or meningitis suggest that there was organic brain involvement as well as meningitis Cryptococcal infections have a strong predilection for the brain and meninges and the infection progresses slowly, over many months but sometimes over years There is usually a low grade fever The small organisms without mycelia may be mistaken for lymphocytes in the spinal fluid It seems likely in view of this long illness ending with a picture of meningitis that if an India ink preparation had been made on the spinal fluid or cultures planted on proper media cryptococcal organisms would have been found Tuberculosis seems less likely in view of the time course of the illness and the long standing evidence of central nervous system involvement with change in personality

ANATOMICAL DIAGNOSIS (Autopsy No 11979) Subacute sphenoid sinusitis chronic purulent basilar meningitis (Torula infection) lobular pneumonia Torula infection of prostate

The dorsal and lateral surfaces of the brain appeared normal Over the base particularly in the interpeduncular fossa there was thickening of the meninges and an old appearing exudate On section the ventricles were a little dilated On microscopic examination the meninges in many places and the choroid plexus showed an alteration which resembled that seen in tuberculous meningitis There were giant cells and radially arranged epithelioid cells around blood vessels but these were inconspicuous compared with the cellular infiltration which produced abscess like areas in the choroid plexus Torula were seen in considerable numbers through the inflamed areas Organisms were also found in the tissue of the prostate at several points where there was an inflammatory reaction

SUMMARY This 57 year old white male received a blow over the left parietal area one year before admission He complained after this of frequent headaches and developed an unusual behavior pattern with poor

memory and mood swings For eight weeks the headaches were more severe and he had attacks of vomiting without nausea These symptoms progressed and the patient became unruly and manic with disorientation Examination showed mild fever disorientation dysarthria blurring of the optic discs and cervical rigidity Exploratory operation revealed no tumor Lumbar puncture released faintly yellowish fluid with 278 mononuclear cells per cu mm 200 mg % protein and 35 mg % glucose Cultures were sterile The course of the illness and the findings suggested some type of inflammatory disease with meningeal involvement and organic brain damage as well The so called lymphocytes in the spinal fluid were undoubtedly cryptococcal organisms which were found at autopsy to be the cause of the illness The sphenoidal sinusitis probably accounted for the early headaches and provided the portal of entry for the TORULA organisms

II

(#415724 Admitted March 13 1947 Died March 16, 1947)

THIS 54 year old Negro laborer entered because of headaches followed by delirium In August 1946 he had a large epistaxis and during the next two months had five similar episodes He was told he had hypertension He was generally nervous and two weeks before admission developed severe con stant aching in the parietal and frontal regions also felt in his neck Four days before entering the hospital he began to talk irrationally He com plained of double vision developed fever and perspired profusely He became increasingly lethargic and had some twitching

PHYSICAL EXAMINATION on admission T 103 2 P 100 R 18 BP 120/86

The patient was in a semi delirious state with Cheyne Stokes respiration There was no lymphadenopathy The pupils reacted normally The heart was normal and the lungs were clear No masses were felt in the abdomen The neck was stiff and the Kernig sign positive The head was turned to the left There was tremulousness of the tongue facial muscles and extremities The fundi were normal There was abducens paralysis on the left and partial abducens weakness on the right The response to painful stimuli was normal No localized weakness change in muscle tone or atrophy was noted Reflexes showed no abnormalities

COURSE IN THE HOSPITAL The temperature remained around 103 with a relative bradycardia There was little change until March 16 when respiration became irregular and the patient died He had received penicil lin No localizing neurological signs appeared

LABORATORY DATA Blood serologic test for syphilis was positive 45 units Urine showed 2 plus albumin 3–5 red and white cells per high power field no casts No anemia or jaundice Leukocyte count was 10 000 with 5% juvenile neutrophils 68% segmented neutrophils 20% lympho cytes and 6% monocytes There was no sickling Blood nonprotein nitro gen was 70 mg% fasting blood sugar 146 mg% chloride 92 mEq CO_2 combining power 24 mEq Spinal fluid examination showed initial pressure 400 mm water normal dynamics 800 cells per cu mm 62% white cells with 77% lymphocytes Pandy 4 plus Mastic 33443210000 Wassermann reaction strongly positive down to 0 1 ml cultures sterile no bacteria on Gram or acid fast stain X ray of skull was normal Chest x ray showed heart and lungs clear Aorta was dilated and tortuous

DISCUSSION This patient had the clinical picture and spinal fluid findings of an acute leptomeningitis There was pleocytosis consisting

mainly of mononuclear cells with moderate elevation of protein and strongly positive blood and spinal fluid serologic test for syphilis in the presence of normal dynamics Important was the absence of demonstrable bacteria on smear or culture of the spinal fluid The duration of the acute phase of the illness was a little over two weeks although the patient had complained for several months of nervousness

In the absence of trauma or disease of the sinuses or ears with the mononuclear cell reaction and the sterile cultures one may discard as possibilities the common types of bacterial meningitis One cannot easily exclude tuberculous meningitis lymphocytic choriomeningitis or a fungus infection One must also consider vascular lesions such as cerebral thrombosis embolism hemorrhage or subdural hematoma and a meningeal reaction produced by an abscess near the surface of the brain or associated with an intracranial tumor

The story of repeated epistaxis the history of hypertension the moderately rapid course and the suddenness of the terminal event *point to some underlying vascular lesion Strongly against embolism* or thrombosis with infarction and secondary meningeal reaction is the absence of any localizing sign except the bilateral sixth nerve palsy the manner of onset the marked febrile response and the prominence of the meningeal reaction It is often difficult to rule out a subdural hematoma The moderately slow onset of symptoms and the sudden termination in the absence of significant localizing signs make one suspicious of this diagnosis A meningeal reaction of this degree would be exceptional The heart was normal on examination and no hypertension was recorded No source for the development of a cerebral abscess was encountered

Acute lymphocytic choriomeningitis is most likely to be confused with tuberculous meningitis The two diseases may be indistinguishable until recovery settles the diagnosis in favor of the benign disorder The onset of symptoms is usually more acute in lymphocytic choriomeningitis

Mycotic infection of the meninges may occur in actinomycosis blastomycosis and torulosis These infections are uncommon and the course is usually more chronic Tuberculous meningitis is a rare disease at this age and there was no tuberculosis elsewhere except possible renal involvement The time course of the illness and the clinical findings are quite compatible with tuberculous meningitis *The high reagin titer in the cerebrospinal fluid does not prove a diagnosis* of central nervous system syphilis Scott Reynolds and Mohr noted the development of this finding in seven cases of meningitis

known not to be due to syphilis of the meninges or nervous system However the history of nervousness for several months the tremulousness and the mental confusion before coma developed, as well as the spinal fluid findings, indicate syphilitic meningo encephalitis as a strong possibility The strongest argument against it is the failure of the patient to respond to penicillin This cannot be considered as conclusive evidence in view of the severity of the illness when treatment was instituted The dilated and tortuous aorta may have been the result of syphilis Altogether the final decision is difficult to make but the evidence seems to favor tuberculous meningitis It is possible that the urinary findings were due to renal tuberculosis

ANATOMICAL DIAGNOSIS (Autopsy No 20478) Bilateral apical scars lungs Fibrocaseous tubercles kidney with erosion into a calyx Localized caseous pyelitis Focal necroses with calcification and regeneration, renal tubules Chronic cystitis and prostatitis with squamous metaplasia in prostate Tuberculous meningitis Internal hydrocephalus Syphilitic aortitis Focal syphilitic nephritis Intrarenal arteriosclerosis Renal scars Chronic superficial ulcer ascending colon Lobular pneumonia

In the lungs there were only old apical scars Fresher lesions were seen in the kidneys with caseous lesions which had ruptured into the pelves producing localized caseous pyelitis There were also scars due perhaps in part to healed pyelonephritis but some were vascular scars No lesions were seen in the cerebral tissue but the meninges showed a widespread tuberculous meningitis In places this was caseous but for the most part the cells were mononuclear and well preserved Tubercle bacilli were stained in these lesions The meninges at the base in general showed more marked involvement than over the cortex but there was striking thickening over the frontal lobes There was a moderate hydrocephalus with a cerebellar pressure cone A terminal lobular pneumonia was present

SUMMARY This 54 year old Negro male had complained for two weeks of severe frontal and parietal headaches and four days before admission became irrational and developed diplopia He complained of general malaise profuse sweating and fever becoming increasingly lethargic 48 hours before entering the hospital Examination revealed high fever relative bradycardia signs of meningeal irritation a pleocytosis consisting mainly of mononuclear cells with moderate elevation of protein content Blood and spinal fluid serologic tests for syphilis were strongly positive No bacteria were demonstrated on smear or culture of the spinal fluid The main possibilities were lymphocytic choriomeningitis mycotic infection syphilis and tuberculosis The time course and the clinical findings were compatible with tuberculous meningitis The lack of a favorable response to penicillin therapy was against a diagnosis of syphilis In a patient with a positive blood serologic test for syphilis meningeal inflammation due to other infections may cause the cerebrospinal fluid reaction to become positive Autopsy revealed fibrocaseous renal tuberculosis and TUBERCULOUS MENINGITIS

III

(#501029 Admitted May 12 1949 Died May 31, 1949)

THIS 28 year old Negro laborer complained of nausea vomiting and lethargy He was rejected for military service in 1945 because of a tumor of the stomach

Two weeks before admission he noted the gradual onset of weakness and fatigability with occasional attacks of vomiting Five days later pain developed in the occipital and nuchal regions Although oriented and responsive when aroused he slept most of the time One week before entering hospital he vomited all fluid and food Later dysphagia and dys arthria were noted and he developed a cough productive of mucoid sputum He sweated but had no chills There was substernal pain on inspiration

PHYSICAL EXAMINATION on admission T 101 8 P 120 R 24 B P 160/90

The patient had lost weight and was lethargic The temporal and malar regions were sunken The pupils reacted normally The left optic disc was hyperemic and edematous Adjacent to the disc there was a linear hemor rhage There was cervical rigidity The lungs were normal The heart rate was rapid and a soft blowing systolic murmur was heard There was slight adenopathy in the epitrochlear and inguinal regions The abdomen was distended and there was a hard superficial movable non tender mass in the right side of the abdomen which was grossly nodular and extended from above the umbilicus to the anterior superior iliac spine It descended on deep inspiration The liver spleen and kidneys could not be felt The prostate was normal The positive neurological findings included the cervical rigidity hoarseness and indistinctness of the voice papilledema on the left weakness of the right external rectus muscle and absent deep tendon reflexes in the lower extremities

COURSE IN THE HOSPITAL The tachycardia continued and the tem perature ranged up to 102 4 for two weeks reaching 104 a few days before death He received penicillin and streptomycin He had difficulty in swallowing May 14 the liver edge was palpated 4 fingerbreadths below the costal margin On May 16 a catheter was placed intrathecally to facilitate the administration of streptomycin The patient s lethargy deepened and he became incontinent of urine An inequality of the pupils was noted On May 27 he had diminished sensation over the entire body and was unable to move his legs which were flaccid and completely areflexic

LABORATORY DATA Blood serologic test for syphilis was negative

Leukocyte count was 11 700 with 10% juvenile neutrophils and 85% segmented neutrophils There was no anemia Urine had a specific gravity of 1 020 albumin was 2 plus and there were 2-3 white and 10-15 red blood cells per high power field with an occasional granular cast Stool showed a positive test (guaiac) for occult blood Blood nonprotein nitrogen 63 mg % phosphorus 5 8 mg % CO_2 combining power 20 mEq sodium chloride potassium and alkaline phosphatase activity were normal Tuberculin test (OT 1 100 000) was strongly positive Spinal fluid on May 12 showed initial pressure 450 mm water normal dynamics 360 cells 90% mononuclear bacterial stains and cultures (including those for acid fast and mycotic organisms) negative glucose 40 mg % (simultaneous blood glucose 86 mg %) chloride 126 mEq protein 50 mg / Wassermann reaction negative Skull x rays showed no abnormalities On chest film the heart and aorta were normal There was a mass to the right of the aorta extending upward with some punctate infiltration into the right upper lung field The remaining parenchyma was normal In an abdominal film the right side was obscured by a large mass Barium enema revealed no gross lesion in the large intestine

DISCUSSION There are numerous diseases which could have evoked this mononuclear cell reaction in the spinal fluid (1) virus infections (2) syphilis (3) acute bacterial meningitis (4) mycotic dis ease (5) tuberculosis (6) neoplasm and (7) some other space occupying lesion such as a subdural hematoma

There is no clinical evidence to suggest that the patient had paro titis or lymphopathia Lymphocytic choriomeningitis is usually a more benign disease None of these possibilities could account for the associated findings Syphilis seems well excluded since serological examinations of the blood and cerebrospinal fluid were negative and the expected therapeutic response to penicillin did not take place

The spinal fluid findings would be most unusual for any type of acute bacterial meningitis and cultures and smears revealed no organ isms Fungi were looked for in specially stained material and cultures on special media revealed no growth

The patient was treated as though he had tuberculous meningitis The clinical course was compatible with this disease and although no tubercle bacilli could be found the tuberculin test was strongly positive The sweats fever chest lesion abdominal mass and the spinal fluid abnormalities could all be encompassed by a diagnosis of tuberculosis However streptomycin both intramuscularly and intrathecally did not favorably influence the clinical course Either there were tubercle bacilli which were not affected by the strepto mycin or the patient had some other disease A primary cerebral neoplasm seems unlikely, as such neoplasms do not often metastasize

widely and one would have to seek another explanation for the medi astinal and abdominal masses However metastasis in the nervous system from cancer elsewhere is not unusual and such lesions when near the surface may set up a meningeal reaction The cranial bones the brain and meninges are all liable to attack Almost any area of the brain itself may be involved the most common being the frontal and temporal lobes cerebellum and choroid plexus but also the pineal pituitary and other sites may be affected In view of the mass projecting from the right hilar region it should be noted that lung cancers frequently metastasize to the brain and nervous system ab normalities may be the presenting clinical manifestation Spread to the brain from tumors of the pleura stomach intestinal tract liver kidney testis prostate and urinary bladder must be considered The mass in the abdomen from its location might well be a metastatic lesion from a small tumor of the testis Hypernephroma is important to consider There was a prominent febrile reaction which is common with this neoplasm and hematuria was present The large abdominal mass did not seem to be connected with the colon or liver

Although there was no leukocytosis this could have been a meta static brain abscess with the primary focus either perirenal or pul monary There was a cardiac murmur but bacterial endocarditis with a ruptured cerebral mycotic aneurysm seems unlikely

Since the abdominal mass seemed to be posterior and lateral one must include among the final list of possibilities lymphosarcoma hy pernephroma testicular tumor and bronchogenic carcinoma It would be unusual for lymphosarcoma to present in this way but it is difficult to rule it out on any other grounds Kidney or testicular tumor metastasizing to the chest would be expected to involve the lung as well as the mediastinal lymph nodes The thoracic mass is com patible with carcinoma of the bronchus The abdominal mass would be difficult to explain on this basis unless it consisted of mesenteric nodes A neoplasm of some type with invasion of the nervous system and meninges seems the most likely diagnosis but the primary site is difficult to predict Statistically a sarcoma is more probable than a carcinoma

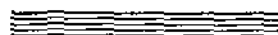
Anatomical Diagnosis (Autopsy No 21832) Lymphosarcoma (large cell type) diffusely involving lymph nodes intestine kidneys left adrenal pancreas (with dilatation of ducts and acini) gallbladder testes heart lungs thyroid muscle bone marrow hypophysis brain cord and meninges with history of meningeal symptoms Purulent bronchitis Lobular pneumonia Pulmonary edema

There was a mass of gray lymphoid tissue measuring 6 cm in diameter

beneath the bifurcation of the trachea A single white nodule 2 cm in diameter projected under the liver capsule The omental fat hanging from the stomach showed irregular confluent areas of thickening suggesting tumor infiltration There was thickening of the mesenteric attachments of the jejunum Starting about 20 cm above the ileocecal valve the ileum became diffusely infiltrated with white tumor which obscured the architecture of its wall There was a mass of confluent tumor filled lymphoid tissue about the cecum The kidneys were swollen and increased in size Numerous nodules of tumor projected from the cut surfaces and in some of these there was hemorrhage

The leptomeninges were opaque This was prominent over the frontal and parietal lobes and less marked over the occipital lobes The ventricular system was slightly dilated Microscopic examination showed this tumor to be a lymphosarcoma with lesions in virtually every tissue except the spleen Massive meningeal involvement gave rise to the clinical picture suggestive of tuberculous meningitis Not only were there perivascular infiltrations in the brain extending from meningeal vessels but there were infiltrations in the white matter basal nuclei and cord The terminal event was caused by aspiration of gastric material which plugged the bronchi

SUMMARY This 28 year old Negro male noted the gradual onset of weakness and fatigability followed by occipital headache vomiting lethargy cough dysphagia dysarthria sweating and substernal pain on inspiration Examination revealed fever evidence of weight loss increased intracranial pressure meningitis a hilar lesion and an abdominal mass There was a mononuclear cell pleocytosis reduction in spinal fluid sugar and cultures of the fluid were sterile The tuberculin skin test was positive The patient was treated with penicillin and streptomycin without benefit The course of the illness and the associated findings led to a diagnosis of tumor involving the nervous system and the meninges primary site undetermined Autopsy revealed a widespread LYMPHOSARCOMA which had invaded the brain spinal cord and the meninges



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Chapter 13

SPECIAL DIAGNOSTIC PROBLEMS

Including the Diagnosis of Certain Rare Diseases

THE GROWING list of diseases which can be cured or favorably modified makes early and accurate diagnosis increasingly important As mistakes in diagnosis are revealed at the operating table or in the autopsy room certain diseases are found to appear with considerable frequency After elimination of the errors which are due to inadequate or incorrect information one finds that the remaining mistakes frequently occur in cases which may present no major feature of the type utilized in previous chapters for orienting the diagnostic analysis Some of these are relatively unusual forms of common diseases such as tuberculosis or syphilis others are rare diseases such as porphyria or amyloidosis Diseases such as hemochromatosis periarteritis nodosa and systemic lupus erythematosus may involve many organs simultaneously or in succession and give rise to a series of manifestations which are difficult to relate one to another Or they may involve one organ predominantly and simulate diseases which ordinarily attack only a single organ As examples we may cite three patients with periarteritis nodosa seen in recent months the first had only constitutional symptoms—fever leukocytosis and loss of weight and strength the second had chronic diarrhea and potassium deficiency the third had bladder symptoms and was considered for many weeks to have a non specific hemorrhagic cystitis

At times a localized disease through the development of complications gives rise to constitutional or remote manifestations which direct attention away from the primary site The following is an example of this type of problem A 39 year old woman developed vomiting and pain about the umbilicus She was febrile and dysp-

neic The abdomen was distended tender, and rigid Pelvic examination revealed a mass apparently a myoma in the anterior wall of the uterus and there was tenderness on both sides of the pelvis She had a pronounced anemia and leukocytosis Diffuse clouding developed over the right lung field and xanthochromic fluid was withdrawn from the pleural cavity The superficial lymph nodes became enlarged A firm irregular mass gradually extended from the pelvis into the lower abdomen Fever continued and more fluid was withdrawn from the pleural cavity The patient died eight weeks after onset of the illness Several clinical diagnoses were entertained (1) peritonitis due to pancreatitis, (2) tumor of the ovary with peritoneal implants (3) pleural effusion secondary to a subdiaphragmatic abscess (4) myomata uteri Autopsy revealed a large myoma of the uterus and a pyosalpinx The tubal infection had invaded the peritoneum and the pleural effusion was secondary to the peritonitis

In some cases the correct diagnosis cannot be determined even with the most intelligent utilization of all the information available However in others the correct diagnosis is not even thought of because of the rarity or unusual features of the problem at hand There is no certain way to avoid mistakes but a systematic approach may help to minimize them A list of diseases is presented in Table 22 which may be consulted whenever a puzzling diagnostic problem is encountered This tabulation has been found helpful in bringing to mind diseases which have a tendency to elude the observer It includes a number of diseases which although rare can be successfully treated when recognized The list is not considered to be complete but it serves to emphasize the potential value of this approach to difficult diagnostic problems Often in our experience the correct diagnosis has been brought to light in this manner

Certain of the diseases listed in Table 22 will be discussed in some detail in the sections which follow Illustrative cases have been chosen for presentation with view to emphasizing certain features in the natural development of the diseases concerned A comprehensive knowledge of the evolution of the various diseases is necessary if they are to be recognized at the earliest possible stage In the early phases of an illness there may be no clear cut objective findings to orient the consideration of the diagnostic possibilities Under these circumstances a review of the relatively rare and frequently misdiagnosed diseases included in Table 22 may suggest fruitful lines of investigation and make one more alert for telltale developments

Table 22 Diseases Which May Be Overlooked in Obscure Diagnostic Problems

- I Tumors and granulomatous diseases
  - A Local
    - 1 Meningioma
    - 2 Parathyroid adenoma
    - 3 Bronchial adenoma
    - 4 Myxoma or thrombus in auricle
    - 5 Pancreatic islet cell tumor
    - 6 Pheochromocytoma
    - 7 Tumor of ampulla of Vater
    - 8 Extramedullary cord tumor
    - 9 Herniated nucleus pulposus
    - 10 Subdural hematoma
    - 11 Hypernephroma
  - B General
    - 1 Myelomatosis
    - 2 Leukemia
    - 3 Disseminated Hodgkin's disease
    - 4 Eosinophilic granuloma
    - 5 Sarcoidosis
- II Infections
  - A Local
    - 1 Infected abortion
    - 2 Abscess
      - a Hepatic
      - b Brain
      - c Epidural
      - d Perinephric
      - e Psoas
      - f Other
    - 3 Tuberculosis
      - a Pericardial
      - b Intestinal
      - c Adrenal
    - 4 Appendicitis
    - 5 Actinomycosis
  - B General
    - 1 Disseminated tuberculosis
    - 2 Syphilis
    - 3 Bacterial endocarditis
- III Endocrine metabolic and nutritional disturbances
  - A Local
    - 1 Hyperthyroidism
    - 2 Addison's disease
    - 3 Myxedema
    - 4 Ectopic pregnancy
    - 5 Inadvertent gastroileostomy
    - 6 Intestinal lipodystrophy
  - B General
    - 1 Porphyria
    - 2 Primary amyloidosis
    - 3 Macrocytic anemia due to intestinal stricture or blind loop
    - 4 Microcytic anemia due to undetected gastrointestinal bleeding
      - a Carcinoma of colon
      - b Hiatus hernia
    - 5 Vitamin D intoxication
    - 6 Hemochromatosis
- IV Connective tissue diseases
  - 1 Systemic lupus erythematosus
  - 2 Periarteritis nodosa
  - 3 Allergic reactions to therapeutic agents
  - 4 Early scleroderma or scleredema
- V Congenital defects
  - 1 Meckel's diverticulum
  - 2 Duodenal diverticulum
  - 3 Coarctation of the aorta

TUMORS AND GRANULOMATOUS DISEASES

The word tumor used in the broad sense indicates not only neo plastic masses but other lesions which are space occupying Tumors may produce symptoms (1) by their invasiveness as with certain malignant growths (2) by pressure symptoms as with a subdural hematoma (3) by the production of an excess of physiologically active material as with a pheochromocytoma (4) by blockage of a conducting organ such as the urethra the colon, or an artery (5) by necrosis with the production of fever and other toxic symptoms or (6) by erosion of blood vessels with resulting hemorrhage as with gastric carcinoma Hemorrhages may also occur into the tumor itself causing sudden increase in size with resulting pressure effects The systemic reaction which accompanies either hemorrhage or necrosis may exhibit not only fever but leukocytosis and elevation of the sedi mentation rate mimicking infection Malignant tumors may invade and replace vital structures and thus interfere seriously with their function This is exemplified by the anemia which develops after widespread invasion of the bone marrow by multiple myeloma or carcinoma So called benign tumors as well as malignant neoplasms if not recognized early may lead to death as for example when there is ulceration and hemorrhage from a colonic polyp or endo crine effects which lead to serious damage to other organs Examples of the latter are the irreversible renal damage that occurs with para thyroid adenoma heart failure due to hypertension in a patient with a pheochromocytoma and hypoglycemia with irreversible central nervous system damage caused by an insulin producing pancreatic tumor Recognition of benign tumors is also important from the viewpoint of their malignant potentialities as illustrated by the fre quency with which cancer develops in cases of colonic polyposis It is often assumed that if symptoms have been present for more than a few months a malignant neoplasm is unlikely However some malignant tumors may grow almost imperceptibly while producing disturbances in function over a period of years As an example in a recent case a brain tumor had produced evidences of hypothalamic dysfunction for more than ten years Certain lymphomas may cause an illness extending over long periods of time and the relatively lengthy course of chronic leukemias and myelomatosis is well known The careful taking of the history and a meticulous physical examina tion with appropriate follow up of any significant leads are still the most vital factors in the early recognition of malignant neoplasms These tumors with their insidious development may simulate func

tional disease mild infection and other seemingly minor maladies so that they remain hidden from the unwary physician

Extravasated blood may collect between the dura and the pia mater after the most trivial injuries In a large number of such cases even careful questioning brings to light no history of cranial trauma and the *subdural hematoma* may escape detection for weeks or even months In the absence of detectable objective evidences of the lesion peculiar behavior on the part of the patient may furnish the only clue Intracranial decompensation may take place with great suddenness In addition to the manifestations already noted there may be intermittent headache a mild hemiparesis or facial weakness alone Papilledema is rarely seen until late but minor ocular mani festations such as inequality of the pupils may be noted earlier in the course of the illness In most instances roentgenograms of the skull examination of the spinal fluid and the electroencephalogram are not diagnostic In suspected cases burr holes should be placed in each side of the skull

Meningiomas compress but do not invade the brain substance They usually develop in patients over 30 years of age and make up about 15 per cent of all primary brain tumors They usually are located above the tentorium in the parasagittal area the olfactory grooves or along the sphenoid ridge The tumor may stimulate the adjacent bone to overgrowth with resulting increase in local vas cularization detectable on x ray examination

Certain infections may also lead to *intracranial tumor* formation and are difficult to distinguish from primary or metastatic neoplasms unless there are other evidences of the underlying infectious process In this category are tuberculomas brain abscess gummas and the parasitic granulomas which may develop in schistosomiasis cysti cercosis and echinococcus disease

Extramedullary *spinal cord tumors* are usually benign and encap sulated If diagnosed early they are removable before irreversible damage is done The earliest manifestation is often pain due to com pression of nerve roots The pain is not always recognizable as nerve root pain but may be vague and inconstant and in the absence of objective findings its cause may remain unsuspected Certain char acteristics of nerve root pain are worth noting at this point It may be severe or mild constant or intermittent and may be recognized by the patient over only a portion of the segmental distribution of the root of origin It may precede other symptoms by months or even years A patient who recently came to operation with a lipoma com

pressing the cord had had intermittent pain attributed to gallbladder disease for eight years before signs of cord compression developed The pain is often increased in severity by factors which increase the cerebrospinal fluid pressure such as coughing, sneezing straining and lifting It may also be more severe when the patient lies down As the compression increases manifestations due to involvement of the long fiber tracts beginning with the pyramidal system appear The presence of a sensory level is an important finding as are elevation of spinal fluid protein content and the presence of partial block with xanthochromic fluid Tumors of the cervical cord may produce abnormal function in all four extremities and may be mistaken for a degenerative disease such as amyotrophic lateral sclerosis

Of particular interest are those benign tumors of the parathyroid pancreas and adrenal which produce an excess of physiologically active hormone *Parathyroid adenomas* are usually limited to one gland and are in most instances benign They may develop in ectopic glands Hyperparathyroidism does not always cause clinically detectable disease of bone It may manifest itself through the formation of renal calculi leading to the development of renal insufficiency Characteristically the serum calcium is elevated and the inorganic phosphorus level reduced unless renal damage has resulted in phosphorus retention The early manifestations may include polyuria and polydipsia due to the calciuria In the differential diagnosis consideration must be given to multiple myeloma metastatic malignancies sarcoidosis hypercalcemia associated with renal insufficiency prolonged milk or alkali ingestion and vitamin D intoxication as well as the various conditions which lead to secondary hyperparathyroidism

The recognition of *hyperinsulinism* assumes importance because of the functional changes which take place in the nervous system and which may rapidly become irreversible during periods of sustained hypoglycemia The symptoms associated with hypoglycemia vary greatly depending on the level to which the blood glucose falls the rate of fall and the individual susceptibility of the patient In patients with true hyperinsulinism due to an *islet cell tumor* of the pancreas the attacks are periodic and tend to increase in severity as the disease progresses Attacks may be precipitated by withholding carbohydrates Subclinical attacks may lead to an increase in appetite and a considerable gain in weight In functional hypoglycemia without islet cell tumor the fasting blood glucose level is usually normal while the hypoglycemia follows the ingestion of carbohydrate

Pheochromocytomas may be associated with intermittent or constant secretion of epinephrine and norepinephrine These tumors are usually unilateral encapsulated and benign In about 10 per cent of the cases they are bilateral or are located in tissue outside the adrenal gland In general the patients have recurrent attacks of hypertension which may end fatally with cerebral hemorrhage or heart failure with pulmonary edema Other evidences of hyperadrenalism are hyperhidrosis glycosuria and leukocytosis as well as a picture which may simulate hyperthyroidism When there is persistent hypertension it is difficult to distinguish these cases from those in which the hypertension is due to other causes Diagnostic tests with histamine to stimulate a paroxysm of hypertension and with piperoxan or phentolamine to abolish the persistent type of hypertension may be helpful but are not infallible One case has been seen in which there was fever leukocytosis abdominal symptoms and glycosuria without hypertension There was loss of weight and a high pulse pressure suggesting hyperthyroidism All of these manifestations disappeared with removal of the adrenal tumor These tumors occur most commonly between the ages of 30 and 60 Previously thought to be very rare the incidence of these tumors has shown an apparent increase with improvements in methods of diagnosis

Bronchial adenomas are frequently highly vascular tumors which are most commonly encountered in young individuals and produce intermittent obstructive symptoms and occasionally massive hemoptysis It may be difficult to distinguish clinically between these benign tumors and a carcinoma arising from the bronchial epithelium Many of the malignant pulmonary neoplasms are not detectable on bronchoscopy When a carcinoma of the lung develops in the superior sulcus pulmonary symptoms may be absent The earliest symptom is usually pain resulting from involvement of nerve roots The first indication of a pulmonary carcinoma may be unresolved pneumonia with or without demonstrable evidence of bronchial obstruction All cases of pneumonia particularly those which are in any way atypical should be followed until there is complete clearing both of the physical signs and of x ray shadows

An uncommon tumor but one of great diagnostic importance is *carcinoma of the ampulla of Vater* Although this neoplasm usually grows quite slowly, it may be accompanied by inflammation and edema which cause obstructive jaundice while the tumor itself is still very small In the early stages the icterus may be intermittent and accompanied by chills and fever simulating intermittent common duct

obstruction by a gallstone As the disease progresses the jaundice becomes constant but may still fluctuate in intensity With involvement of the duodenal mucosa there may be occult blood in the stools It may be very difficult to recognize this type of tumor at operation particularly if surgery is undertaken as it should be early in the course of the illness There may be only mild to moderate dilatation of the common duct and the tumor may not be detected unless the duodenum is opened The tumor being soft, a catheter may easily pass through into the common duct without any sense of resistance If calculi are found in the gallbladder and this frequently happens the surgeon may be content with a cholecystectomy

The three cardinal manifestations of renal neoplasms are of course hematuria pain, and the presence of a palpable mass in the flank However when the tumor has reached this stage complete eradication may not be possible A *hypernephroma* may produce systemic manifestations out of proportion to its actual size In cases of unexplained fever the possibility of a neoplasm of one of the kidneys should always be kept in mind If the fever is accompanied by hematuria of even slight degree every possible step should be taken to rule out a tumor of the kidney

Multiple myelomas are characterized by osseous lesions anemia and abnormalities in the protein of the serum and urine Pain is often an early and distressing manifestation but in some cases even with extensive disease no definite abnormalities in the bones can be detected by roentgen examination The anemia may be macrocytic in type the disease picture simulating pernicious anemia Pronounced hyperglobulinemia may develop as well as hypercalcemia With the changes in serum protein the red corpuscles may exhibit a marked tendency to clump and form rouleaux Detection of this phenomenon in routine blood counts may give the first hint of the correct diagnosis In our experience pneumococcal infections have seemed to be relatively frequent complications with a particular tendency toward the development of meningitis and pyarthrosis

Leukemia is easy to recognize when there are typical changes in the blood but not infrequently patients are encountered with normal or low leukocyte counts and little change in the character of the circulating white cells Occasionally changes in the peripheral blood may not appear until six to eight months after onset of the illness On the other hand the *leukemoid reactions* associated with a variety of infections including tuberculosis may be mistaken for leukemia As pointed out by Wintrobe and Mitchell there is no organ or tissue

which has not been involved by leukemic infiltration with or without the production of symptoms In the initial examination of patients with leukemia such different diseases as thyroiditis osteomyelitis tuberculosis bacterial endocarditis pericardial effusion and pelvic tumor have been suspected The degree of lymphadenopathy or splenomegaly may not be sufficient to attract attention and the total leukocyte count and differential count may be essentially normal Severe anemia may give the first suggestion of a blood disorder Atypical cases of leukemia have been divided into several groups by Wintrobe and Mitchell on the basis of the chief presenting symptoms (1) symptoms suggesting an acute inflammatory condition (2) symptoms simulating abdominal or cardiac disease (3) symptoms referable to bones or joints (4) those characterized by skin changes (5) symptoms suggesting disease of the nervous system (6) manifestations directing attention to the chest and (7) symptoms referable to the genitourinary organs Clinical findings which suggest leukemia include (1) nerve root and deep bone pain (2) symptoms and signs of arthritis (3) tumefaction of the gums (4) even slight enlargement of lymph nodes or spleen (5) unexplained fever (6) bone tenderness (7) unexplained purpura or retinal hemorrhages (8) reddish gray non liquefied tissue found at operation for osteomyelitis and (9) unexplained acute enlargement of the breasts and ovaries Important laboratory findings are (1) increase in basal metabolic rate (2) high blood uric acid (3) severe unexplained anemia (4) nucleated red cells diffuse or punctate basophilia or increased reticulocytes in the presence of an otherwise aplastic blood picture (5) unexplained macrocytic anemia (6) leukopenia due to reduction in all types of cells and yet marked by the presence of a few immature cells which may be mistaken for lymphocytes and (7) osteolytic myelosclerotic or tumor like changes in bone x rays Of the blood disorders aplastic anemia is the one most often confused with leukemia Hodgkin s disease myelophthisic anemia from bone metastases and osteosclerotic anemia must also be differentiated from aleukemic leukemia Marrow from sternal puncture often contains a large number of immature leukocytes uniform in type making the diagnosis clear However such a preponderance of a single cell type *is not always found Biopsy of sternal marrow is less likely to be* deceptive

Thannhauser and Magendantz first emphasized that in *eosinophilic granulomatosis* a wide variety of organs including skin osseous tissue dura brain lung pleura liver spleen and lymph nodes may

be involved either alone or in a multitude of combinations The cholesterol accumulation in the xanthomatous cells is not accompanied by elevation of the serum cholesterol level The solitary eosinophilic granuloma in which histiocytic proliferation with accumulations of eosinophilic leukocytes occurs is the early phase of the systemic disease The skin lesions appear usually in the axillas, on the neck and in the antecubital fossae Lesions may also be found in the mucous membranes of the mouth the epiglottis bronchi scleras or vagina leading to ulceration They may resemble petechiae The disease may run its course without the appearance of cutaneous or mucous membrane lesions In any case of diabetes insipidus a careful search should be made for other lesions of Schuller Christian disease since the two are frequently associated Lesions of the bones when present are osteolytic in character and must be differentiated from myeloma neurofibromatosis metastatic bone tumor, and other granulomatous diseases The typical triad of bony defects of the skull exophthalmos and diabetes insipidus occurs most often in children and infants in whom this disease is more fulminating than in adults The generalized type of disease with involvement of lymph nodes liver and spleen is said to be rare in adults

Hodgkin s disease is commoner in the white population than in Negroes and commoner among males than among females It may occur at any age, but is rare in infancy and old age The sarcomatous form is more prevalent in older age groups, particularly between the ages of 50 and 70 The lesions may be restricted to isolated groups of nodes or more commonly predominate in one such group (cervical mediastinal axillary inguinal retroperitoneal, or mesenteric) The consistency of the nodes is variable They may be elastic soft hard or very firm In the early stages lymph node enlargement may be intermittent with subsidence of the swelling for long periods of time In most instances the disease starts with enlargement of a single group of nodes most commonly in the cervical region with a predilection for nodes in the posterior triangle The nodes are not adherent or matted together unless there is a complicating infection or x ray treatment has been given They may be painful At times the tissue will extend through the capsule of the nodes so altering their structure that they are not recognizable as nodes This condition has been designated by Jackson and Parker as Hodgkin s sarcoma The nodes involved may become secondarily infected Hodgkin s disease may become widely disseminated and its distribution may depend predominantly upon the presence of reticuloendothe

lium rather than of lymphoid tissue This would explain its frequent occurrence in structures such as liver and bone marrow which are rich in reticuloendothelium but comparatively poor in lymphoid tis sue The central nervous system largely lacking in both components is rarely the seat of involvement When there is extensive involve ment of the liver a form of portal cirrhosis with portal hypertension may develop as a result of the proliferation of connective tissue Jaundice may occur when enlarged nodes compress the common bile duct Involvement of the nervous system may take place by spread of the process from the dura or pia mater to the cortex the pituitary gland or the spinal cord The process may extend between the ver tebral bodies and by occluding blood vessels and lymphatics lead to destruction of nervous tissue Peripheral nerves are involved more often than is the spinal cord In rare instances there is a miliary spread to the bone marrow leading to a picture of aplastic anemia Dur ing the early phases of the illness and even throughout its course there may be no enlargement of the superficial lymph nodes If the abdominal nodes enlarge there may be gastrointestinal symptoms including persistent pain but in some such cases there are no local symptoms only constitutional manifestations including fever sweats chills weakness and loss of weight Involvement of the gastrointes tinal tract is less frequent in Hodgkin s disease than in lymphosar coma Pain is a prominent symptom when there is involvement of bone Fever is more common when the thoracic or abdominal nodes are involved During the febrile periods there may be an increase in size of the nodes or rapid enlargement of the spleen The hematologic changes are seldom of any aid in diagnosis Occasional severe anemia results from bone marrow involvement Macrocytosis and occasion ally a hemolytic type of anemia are present Leukocytosis may de velop as the disease progresses and leukopenia may be noted in cases with splenic enlargement and with predominant involvement of the retroperitoneal nodes The combination of Hodgkin s disease and tuberculosis is not infrequent Jackson and Parker have separated Hodgkin s disease into three types Hodgkin s paragranuloma is an infrequent and relatively benign form With Hodgkin s granuloma the commonest and most familiar form the progress may be rapid or it may extend over a period of five years or longer In this type the involvement may be restricted to the deep nodes and internal organs so that it is difficult to diagnose and if fever is present it may simulate an infection The third type is Hodgkin s sarcoma, which tends to occur in older age groups invades tissue and neigh

boring organs and runs a fairly rapid course with death usually within one or two years In Longcope s series the diagnoses initially considered included carcinoma of the lung esophageal stricture liver abscess cholelithiasis carcinoma of the gastrointestinal tract duodenal ulcer rheumatic fever pyelitis polyserositis aplastic anemia and brain tumor

Points of difference between *reticulum cell sarcoma* and *lymphosarcoma* are (1) lymphosarcoma may be accompanied by a blood picture of lymphatic leukemia which is rare in reticulum cell sarcoma (2) true lymphosarcoma is never primary in bone, and (3) the main peaks in age incidence of lymphosarcoma are in the 1st and 6th decades while the reticulum cell type occurs chiefly in the 5th 6th and 7th decades Reticulum cell proliferation constitutes the main cellular response to tuberculosis sarcoidosis and syphilis—in general those diseases to which the term granulomatous is commonly applied The giant cells found in the presence of a foreign body are derived from reticulum cells The reticulum cell is identical with the histiocyte clasmatocyte macrophage or large wandering mononuclear cell The reticulum cells are derived from mesenchyme and are known in the nervous system as microglia These cells occur in widely scattered areas and, therefore reticulum cell sarcoma may arise from almost any organ or tissue in the body The most frequent point of origin is in retroperitoneal nodes or the gastrointestinal tract The liver may be involved by direct extension or metastasis When the spleen is affected it is usually quite large in size The invasive and destructive character of the lesions leads to pain often constant and sometimes extreme The nodes are occasionally tender usually firm and may be fixed to the underlying tissues The overlying skin may be thickened and brownish Long continued sore throat is an initial symptom in over 20 per cent of the cases Such a symptom in an elderly patient should always arouse suspicion of malignant disease particularly if associated with bleeding or notable enlargement of one of the tonsils Loss of weight is a frequent early manifestation Systemic manifestations are much less common than in Hodgkin s disease Normochromic or hypochromic anemia is present in about a third of the cases Rarely there is a moderate leukocytosis but never leukopenia We have occasionally observed large mononuclear cells in excessive numbers in the peripheral blood These were thought to be monocytes In primary reticulum cell sarcoma of bone the age distribution differs materially from that of the generalized or soft tissue form of the disease 64 per cent of the patients being under

the age of 40 and 28 per cent below the age of 20 The lesions are found most frequently in the long or flat bones femur clavicle tibia humerus and vertebrae Metastases are late and are seen chiefly in the neighboring lymph nodes Clinically the onset is similar to that of other primary bone tumors the chief symptom being pain not relieved by rest X ray pictures show chiefly bone destruction and to a less degree new bone formation In early cases there may be only mottled destruction of the medulla of the bone

Sarcoidosis is an essentially benign disease The extent of the lesions may vary greatly They may be limited to a few lymph nodes or be widely scattered affecting almost any structure in the body The lesions usually have a tardy evolution with no inflammatory reaction about them They have a pronounced tendency to heal spontaneously but may recur months or years later in the same or another location *Beryllium* compounds produce a granuloma having a similar appearance which may not develop until months or even years after exposure Onset of the disease in sarcoidosis is usually insidious and may develop in a variety of ways including ocular disturbances enlargement of lymph nodes pulmonary symptoms joint manifestations pain in various areas and parotid swelling. On physical examination the nodes resemble those in Hodgkin s disease When the mediastinal nodes are enlarged there is often infiltration in the lungs This occurs more frequently than in lymphomas The pulmonary findings are often noted on routine x ray examinations the patient not being aware of any illness On the other hand in some cases the symptoms of pulmonary insufficiency may be out of proportion to the extent of the lesions seen in the x rays Symptoms of severe pulmonary insufficiency may arise owing to reduced transportation of oxygen across the alveolo capillary membrane There is tachypnea at rest and severe dyspnea on slight exertion When the eye is affected there is usually concomitant involvement of lymph nodes or lungs or both The characteristic involvement of the uveal tract and parotid glands producing so called uveoparotid fever is frequently accompanied by transient paralysis of one or more of the cranial nerves particularly the seventh third eighth tenth or the central branch of the fifth In contrast to tuberculosis there may be extensive involvement of the heart with infiltration through the pericardium and into the myocardium producing conduction defects as well as leading to heart failure The liver is frequently involved occasionally extensively with the development of a picture resembling Laennec s cirrhosis There may be marked elevation of the alkaline phosphatase

activity A form of chronic nephritis may appear during the course of the disease which in many respects resembles glomerulonephritis although the blood pressure may not become elevated Dermal involvement consisting of lesions of many varieties is frequently noted The syndrome characterized by swelling of the soft parts of the nose with nodular enlargements about the joints of the fingers and toes is known as lupus pernio of Besnier Involvement of the muscles may be a prominent manifestation and the disease may begin with symptoms suggesting arthritis The mucous membranes of the nose may be infiltrated and the process may extend to the nasopharynx and even penetrate the cribriform plate Resultant invasion of the pituitary and its stalk or the hypothalamus may cause various types of dysfunction including diabetes insipidus In other instances anterior pituitary destruction may result in a syndrome resembling Simmonds disease There is usually only a mild constitutional reaction in sarcoidosis even though the lesions are widespread Fever if present is seen chiefly during the early stages or in the cases with uveoparotid involvement There may be elevation of serum calcium and frequently elevation of gamma globulin In contrast it is the alpha 2 globulins which are elevated in tuberculosis

INFECTIONS

Fever is one of the most common manifestations of infections and it is frequently the initial symptom However low grade infections may cause little or no fever and under certain circumstances particularly in elderly individuals fever may be absent or only intermittently present even in severe infections The reliability of fever as an index of infection is further vitiated by the fact that it may be encountered in a number of other conditions including neoplastic diseases blood dyscrasias any conditions leading to necrosis of tissue and allergic reactions Febrile reactions to drugs may pose very disturbing diagnostic problems in the treatment of infections The fever associated with these non infectious states may be accompanied by chills leukocytosis and other constitutional manifestations suggesting an infection

Severe generalized infections may have their origin in apparently insignificant localized lesions An example of this is the streptococcal lymphangitis and bacteremia which may result from a small puncture wound of a finger It is not always an easy matter to find the original local infection A patient may have pylephlebitis and bacteremia without having experienced any of the usual symptoms of the acute

appendicitis from which it arose Occasionally the patient may make a deliberate effort to conceal the local infection as frequently hap pens in cases of self induced abortion If the origin of an infection is open to the slightest question it is never safe to omit any step in the physical examination

Although *appendicitis* is in most instances easily recognized by both physician and patient some cases still go unrecognized until fatal complications have developed Among the factors responsible for the variable clinical picture are (1) the size and location of the appendix and (2) the intensity of the local inflammatory reaction Particularly in the aged appendicitis may develop with little or no pain and may be essentially asymptomatic until peritonitis develops Owing to variations in the location of the appendix the pain may be in the right flank or costovertebral angle or it may radiate into the thigh There may be dysuria and radiation of pain into the genitalia when the inflamed appendix causes irritation of the bladder The differential diagnosis may include diseases such as mesenteric lym phadenitis in children Meckel s diverticulitis regional enteritis and neoplasm of the cecum In children pneumonia and in older indi viduals cholecystitis salpingitis torsion of an ovarian cyst ruptured graafian follicle and ureteral stone may at times simulate appendi citis

Actinomycosis is a chronic infection producing granuloma like lesions which may break down and give rise to draining sinuses The lesions usually develop in the cervical facial thoracic or abdominal areas If the diagnosis is not made when the initial manifestations of the disease bring the patient to the physician unnecessary surgical operations may be performed with inadvertent production of chronic sinuses The chronic pulmonary lesions of actinomycosis are fre quently misinterpreted as a pyogenic abscess or tuberculosis The diagnosis is missed most often because there has not been a com plete bacteriological study of material obtained from the lesion De pending on the site and nature of the involvement differentiation must be made from tuberculosis pyogenic abscess regional enteritis neoplasms and other mycotic infections At times this disease may become disseminated although it typically spreads by direct invasion of contiguous structures

The clinical manifestations of *tuberculosis* are so varied and subtle that this disease should be kept constantly in mind in approaching almost any diagnostic problem Few diseases with the prevalence of tuberculosis simulate so many other conditions Some of the prob-

lems encountered in the diagnosis of tuberculosis have been mentioned in previous chapters They will be presented here in a more orderly fashion Clinically there are two types of tuberculosis

(1) A type characterized by fever and other constitutional manifestations but without definite localizing signs
 (a) miliary tuberculosis
 (b) disseminated tuberculosis
(2) Localized tuberculosis with manifestations referable to single organs or tissues such as
 (a) lungs and bronchi,
 (b) serous membranes
 (c) lymphatic system
 (d) nervous system
 (e) kidneys
 (f) gastrointestinal tract
 (g) liver

Subacute or chronic hematogenous dissemination without seeding of the lungs is not uncommon particularly in the Negro race and in children The number of bacilli released at any one period is not overwhelming and the course of the illness may extend over many months There is usually a typhoid like state with high fever without leukocytosis The patient may look reasonably well in spite of the constitutional manifestations Careful search must be made at frequent intervals for the appearance of lesions in the superficial lymphatics or the optic fundi and biopsy of the liver may be indicated The tuberculin reaction may be negative in such cases and in older individuals progressive tuberculosis may be associated with little fever or sense of illness When the picture is one of fever of obscure origin such possibilities as brucellosis systemic lupus erythematosus bacterial endocarditis carcinoma and Hodgkin s disease are frequently under consideration In some instances in which there is evidence of lymphatic system involvement the patient eventually is proved to have both tuberculosis and either systemic lupus erythematosus or Hodgkin s disease

Differentiation of tuberculosis from other diseases in which respiratory manifestations predominate is a common problem A history of constitutional symptoms antedating by a week or more the onset of the pulmonary complaints is very suggestive of tuberculosis Chills cyanosis and grunting respirations rare accompaniments of tuberculous pneumonia are quite typical of other bacterial pneumonias Solidification of an entire lobe is also rare Particularly difficult in the

older patient may be the differentiation from carcinoma of the lung or from chronic pneumonia associated with the aspiration of oily material

Tuberculosis may involve one or more of the serous membranes Infection of the pericardium usually occurs by direct extension from the mediastinal lymph nodes and may lead to constrictive pericarditis with the picture of chronic inflow stasis

Generalized involvement of the lymphatic system is not rare and may be so prominent as to cause confusion with Hodgkin s disease Inflammation of the mesenteric nodes may be the cause of vague but persistent pain particularly in children

Single or multiple tubercles may develop in the nervous system and may produce a mass of sufficient size to cause focal symptoms simulating the varied manifestations of brain tumor In many cases the meninges become involved and care is required in distinguishing these patients from those with other types of meningitis

When the kidneys are involved there are usually manifestations suggesting urinary tract disease According to Herbst renal tuberculosis should be kept in mind when any of the following conditions is found (1) evidence of unilateral renal infection (2) hematuria without obvious explanation (3) pyuria with no organisms demonstrable by ordinary staining methods or culture (4) persistent pyuria of any degree (5) cystitis that does not respond to a reasonable period of treatment and (6) pyuria or dysuria in individuals with a history of tuberculosis or with recognized active extra urinary tuberculosis including nodular lesions in the seminal tract

According to Anderson it is unusual to see tuberculous involvement of the alimentary tract or pharynx except as a complication of cavernous pulmonary tuberculosis He states that the constancy of this relationship suggests that surface contamination is the usual mode of infection particularly in view of the rarity of such lesions in lympho hematogenous tuberculosis The frequency of cecal lesions would be accounted for by the slowness of passage of intestinal contents in this region These facts indicate that the finding of healthy lungs is strong evidence against an oral pharyngeal laryngeal or gastrointestinal lesion being due to tuberculosis when the etiology of such lesions is in question In our experience however gastrointestinal lesions are not infrequently seen when there is no recent or current evidence of active pulmonary disease These lesions may be located in areas other than the ileocecal region and may herald their presence by hemorrhage obstruction or other symptoms Occasion

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Streptococcus viridans vegetations are usually engrafted on valves damaged by chronic rheumatic endocarditis Gonococcal vegetations are frequently found on normal valves but in many instances develop on valves damaged by syphilis In the case of pneumococcal vegetations pre existing valvular disease is the exception rather than the rule At least half of the cases of pneumococcal endocarditis are complicated by acute pneumococcal meningitis In patients with congenital cardiovascular defects vegetations tend to develop in two places (1) either on or in the neighborhood of the valvular endocardium for example on a bicuspid aortic valve or in association with a high interventricular septal defect—bacterial endocarditis is rarely encountered in patients with low interventricular defects or a patent foramen ovale (b) in association with defects involving the arterial wall such as patent ductus arteriosus or coarctation of the aorta Bacterial vegetations have also been found in syphilitic aneurysms at the site of arteriovenous aneurysms and at anastomotic junctions following cardiac surgery

There is a natural tendency for the lesions in subacute bacterial endocarditis to heal In almost every untreated case examined at autopsy one finds lesions in various stages of healing up to complete fibrosis Another point of interest is the frequency with which there is a diffuse glomerulonephritis independent of focal embolic phenomena Severe renal insufficiency may dominate the clinical picture In most instances there is no elevation of the blood pressure When myocardial insufficiency is present the diagnosis of an underlying bacterial endocarditis may be difficult The sudden appearance of myocardial failure in association with fever should suggest this possibility Cerebral emboli are common Localizing signs may not be present and the picture may resemble an encephalitis

The diagnosis of bacterial endocarditis is perhaps most often missed in elderly individuals Emboli may be few the constitutional manifestations are often insignificant and in a patient who develops for example a sudden hemiplegia the mild anemia and cardiac murmur may be discounted in considering the possible causes of the central nervous system disorder

It has been pointed out that when severe mitral stenosis and auricular fibrillation are present bacterial endocarditis is rare This is probably due to the fact that these individuals have a shorter life span than those with minimal valve damage

ENDOCRINE, METABOLIC, AND NUTRITIONAL DISTURBANCES

Diseases involving endocrine organs and leading to either hypofunction or hyperfunction may present difficult diagnostic problems One may become so preoccupied with the clinical evidence of involvement of a local organ system that the manifestations of the basic endocrine disturbance may go unnoticed An example of this type of problem is that presented by *hyperthyroidism* This disease can be easily recognized when the classic manifestations including exophthalmos goiter fine tremor nervousness emotional instability, excessive sweating tachycardia and loss of weight are present However in certain cases the presenting feature may be extensive muscular atrophy while there may be no detectable enlargement of the thyroid and no more than a questionable elevation of the basal metabolic rate Thyrotoxic myopathy is more apt to occur in elderly individuals but any patient with an unexplained neuromuscular disorder should be investigated for underlying hyperthyroidism Similarly in all patients with unexplained cardiac failure or with irregularities in cardiac rhythm or unexplained tachycardia, hyperthyroidism must be considered In other cases the presenting feature may be uncontrolled diarrhea and ulcerative colitis may be suspected The increased metabolic activity in hyperthyroidism may aggravate other underlying diseases and these in turn may mask the thyrotoxic symptoms This is particularly true in cases of diabetes mellitus or cardiac disease Difficulties in diagnosis may also arise in other conditions which lead to increased oxygen consumption such as fever anxiety states certain infections leukemia and pheochromocytoma In these cases in which there is hypermetabolism without hyperthyroidism determination of the protein bound iodine of the serum or the radioiodine uptake may be of value

Myxedema may be as readily overlooked as hyperthyroidism The appearance of the patient, together with the anemia and lethargy may lead to a diagnosis of chronic nephritis There may be vague arthralgia and muscular manifestations which divert attention from the evidence of thyroid hypofunction Myxedema may present with a pericardial effusion In hypothyroidism secondary to interior pituitary deficiency there are usually associated evidences of gonadal and adrenal hypofunction It is important to differentiate this condition from primary myxedema because these patients when given thyroid extract may develop an adrenal crisis Another distinction to be made is that between hypometabolism and hypothyroidism In

most instances hypometabolism without hypothyroidism will not be beneficially influenced by thyroid hormone Here again help in diag nosis may be obtained from the protein bound serum iodine level or the radioiodine uptake or when these are not available from ther apeutic test doses of thyroid hormone In true hypothyroidism sub stitution therapy in small doses will bring function to normal When large doses of the hormone do not produce normal or elevated function the diagnosis of myxedema should be questioned

Adrenal insufficiency in its various stages may also be deceptive from the point of view of diagnosis Neurasthenia of a vague type may lead to a mistaken impression that the patient has a functional emotional disorder Mild crises with fever asthenia vague gastro intestinal disturbances and loss of weight may simulate other chronic disorders In differential diagnosis one should not overlook the salt losing type of nephritis which may give rise to symptoms closely simulating those of Addison s disease Pigmentation characteristic of adrenal insufficiency may be present normally in Negroes Moreover a similar type of pigmentation may occur during pregnancy in cer tain vitamin deficiency diseases such as pellagra in chronic nephritis hemochromatosis scleroderma dermatomyositis systemic lupus erythematosus and exposure to certain metallic poisons

Ruptured *ectopic pregnancy* should always be considered in any patient who after missing at least one menstrual period experiences sudden pain particularly in the lower part of the abdomen This may be accompanied by nausea vomiting fever and leukocytosis The presence of free blood in the peritoneal cavity may lead to diaphrag matic irritation with shoulder tip pain and there may be abdominal tenderness and a palpable mass Prompt diagnosis is imperative as death from hemorrhage may occur quickly

The congenital or light sensitive form of *porphyria* usually presents no problems in recognition The intermittent acute form seen in older individuals may be difficult to diagnose Occasionally cases are en countered in which there is a chronic form of the disease with features common to the other two more distinct types In this mixed type photosensitivity may not appear before adult life The skin lesions may develop after exposure to heat and to trauma as well as to light often presenting a violaceous hue and at times resembling the lesions of scleroderma In the intermittent acute type and mixed types there may be bizarre manifestations referable to the nervous system or gastrointestinal tract Any portion of the nervous system may be affected and there may be emotional symptoms with nervousness

and other psychic abnormalities, including hysterical behavior and delirium Cranial and peripheral nerve involvement are frequently seen and the disease may be confused with other types of acute polyneuritis The onset of activity may be signaled by severe abdominal pain often associated with spasm and rebound tenderness as well as fever Porphobilinogen which is the colorless precursor of the two important porphyrin pigments that appear in the urine is apparently the basic material responsible for the abdominal and the nervous system symptoms The photosensitive type of porphyria is associated with the presence of the red uroporphyrin, which is more readily discovered The possibility of porphyria in the adult should be considered in obscure nervous or emotional disturbances unexplained polyneuritis or bulbar palsy, or abdominal colic of the type seen in gallbladder disease, appendicitis or intestinal obstruction There may be an associated leukocytosis

There are three types of *amyloidosis* (1) the so called secondary type which is associated usually with a chronic suppurative or inflammatory disease such as tuberculosis or osteomyelitis (2) primary amyloidosis in which there is no apparent predisposing disease and which differs from the secondary type in the localization of the amyloid deposits and (3) a variety which occurs in association with certain cases of myelomatosis In the primary type which may present the most difficult problems in diagnosis deposition of the amyloid is in the muscular coat of the medium sized arteries the heart muscle, kidneys at times the liver and spleen and also the mucous membranes particularly of the mouth and conjunctivas Amyloid tumors may form in various places In one recent case the first manifestation was that of a spinal cord tumor which on operation proved to be extramedullary and on microscopic section was found to be composed of amyloid The deposits may be localized to the vascular system and we have seen instances in which there were peculiar cardiac arrhythmias and heart failure The cardiac symptoms may be associated with hypotension which seems related to the extensive amyloid deposits in the medium sized arteries rendering the muscular coats unresponsive to autonomic control The clinical picture in these cases closely simulates that seen in arteriosclerotic heart disease Macroglossia is present in some cases Primary amyloidosis is rarely seen in patients under 50

The use of vitamin D in the treatment of various types of arthritis and to promote the healing of fractures has led to the development of *vitamin D intoxication* in certain patients Serious renal damage

may result from such treatment Suspicion of vitamin D intoxication may be aroused by the discovery of calcium deposits in the mucous membranes about the mouth and in the conjunctivas as described by Walsh and Howard The early manifestations are headache diarrhea anorexia polyuria and lassitude The Sulkowitch test on the urine will be positive as a result of the hypercalciuria

When a *macrocytic* type of *anemia* has been detected it is extremely important to make a thorough search for its cause The findings in the peripheral blood and in the bone marrow are essentially the same *in patients with deficiency of either folic acid or vitamin B_{12}* The macrocytic anemia of true Addisonian pernicious anemia is due to a vitamin B_{12} deficiency whereas the pernicious anemia of pregnancy and that of non tropical sprue are usually associated with folic acid deficiency Macrocytic anemia may also be associated with hepatic disease hemolytic diseases and certain diseases which lead to bone marrow replacement Of importance is the recognition of the macrocytic anemia which develops in the presence of intestinal strictures and blind intestinal loops The accurate diagnosis of vitamin B_{12} deficiency is vital because of the associated central nervous system manifestations which are not benefited by folic acid

A *hypochromic and microcytic anemia* in virtually every instance in the adult is indicative of iron deficiency which is usually due to loss of blood In certain cases the source of the bleeding is difficult to detect The bleeding may be intermittent and the loss at any one time may be small These patients should be carefully screened for the presence of a diaphragmatic hernia esophageal varices peptic ulcer diverticula or polyps of the intestines and neoplasms of the stomach or colon even though no blood can be detected in the stool by the most sensitive methods

Hemochromatosis is characterized by the deposition of iron in the tissues leading to fibrosis and functional impairment of the organs involved Recent studies have led to the differentiation of three types (1) so called idiopathic hemochromatosis (2) transfusion hemochromatosis due to the liberation and deposition of more iron than can be excreted and (3) dietary hemochromatosis There is little difficulty in making the diagnosis when the cardinal manifestations—cutaneous pigmentation liver enlargement and diabetes mellitus—are present The bronzing of the skin associated with melanin deposition may simulate that seen in adrenal insufficiency In other instances it has a more grayish appearance The mucous membranes may be involved The characteristic physiological abnormalities are an elevation of the

serum iron content and a saturation of the capacity of the serum for binding this metal Apparently the only organic lesion which appears in all instances is a pigment cirrhosis of the liver Hence liver biopsy is the most reliable means of establishing the diagnosis Bronzing of the skin may be absent in about 20 per cent of the cases, and it is when there is widespread organ involvement without this classic manifestation of the disease that other entities may be simulated

CONNECTIVF TISSUE DISEASES

Systemic lupus erythematosus is a constitutional disease of un known etiology producing widespread degenerative changes in small blood vessels and connective tissue involving chiefly the ser ous and synovial membranes the kidneys the heart and the dermis The initial manifestations may be fever and weakness The fever varies in type but may be severe with wide daily fluctuations suggest ing an infection Evidences of involvement of the serous and synovial membranes are frequent and include arthralgia, pleuritis pericarditis and abdominal pain The joint pains may be migratory and may or may not be associated with objective changes There may be effusion into serous cavities The heart may be involved tachycardia and a gallop rhythm, particularly during febrile episodes are usually indic ative of myocardial disease The superficial lymph nodes are fre quently enlarged The spleen however is usually not palpable The cutaneous lesions are variable in type and some cases may run their entire course without there being any dermal manifestations Ery thematous lesions which are elevated and which may be discrete or confluent are often seen The most characteristic locations for skin lesions are the bridge of the nose and the malar eminences Erythem atous lesions may develop about the base of the nails and on the soft pads of the fingers Petechiae and even hemorrhagic vesicles have been described Urticarial lesions with or without angioneurotic edema may be noted Vascular lesions can be recognized in the eye grounds where hemorrhages and the fluffy exudates known as cytoid bodies may appear The blood pressure is usually normal throughout the illness even in the presence of extensive renal damage The clin ical course is usually characterized by periods of remission alternating with periods of activity but the disease may be quite localized during some of the exacerbations For instance in one exacerbation there may be fever and arthritis while in another there may be only cuta neous lesions In this manner the illness may go on over a period of

many years However in some cases the process is more fulminating and death occurs in a few weeks or months without any intervening remission On many occasions we have seen patients with chronic discoid lupus develop the full blown systemic disease Patients with lupus are susceptible to infections particularly of the respiratory and urinary tracts Hence whenever fever and evidence of active disease develop in a patient with systemic lupus it may be difficult to tell whether there is reactivation of the underlying disease or a complication due to some type of infection Leukopenia is a common manifestation of lupus The urine often contains red cells white cells and casts as well as albumin Moderate to marked thrombocytopenia may occur and occasionally the presenting manifestation of the disease is thrombocytopenic purpura Other abnormalities of the blood may develop including severe hemolytic anemia A false positive serologic test for syphilis is a common finding and other abnormalities of the blood proteins may be encountered as evidenced by elevation of serum gamma globulin positive thymol turbidity test and positive cephalin cholesterol flocculation test Experience now suggests that the finding of typical L E cells is strong evidence for the diagnosis of systemic lupus erythematosus However in many cases these cells cannot be found even during the active stages of the disease

Periarteritis nodosa may affect the medium sized and small arteries in any area of the body The commonest manifestations are fever edema systemic arterial hypertension albuminuria and hematuria In the beginning the intensity of the symptoms and signs may vary with periods of remission and exacerbation The following features of an illness should arouse suspicion of periarteritis nodosa (1) a subacute or chronic febrile illness for which no causative infectious agent can be found (2) atypical abdominal symptoms when the clinical and x ray studies do not reveal any local abnormality (3) recurrent attacks of abdominal pain and diarrhea associated with potassium deficiency (4) an illness suggesting primary renal disease or (5) a combination of symptoms suggesting polyneuritis and polymyositis A variety of cutaneous manifestations may develop including urticaria angioneurotic edema and eruptions resembling scarlet fever and in some cases actual necrosis and ulceration of the skin The earliest symptom may be bronchial asthma accompanied by a conspicuous eosinophilia Leukocytosis is commonly present and when combined with fever often leads to a suspicion of some type of infection such as brucellosis In contrast to systemic lupus ery

thematosus, abnormalities in serum globulin or a biologic false positive test for syphilis rarely occurs in periarteritis nodosa

In typical instances scleroderma and dermatomyositis are easily recognized However in the early stages diagnosis may be difficult unless one is familiar with the various ways in which these diseases may begin The earliest evidence of *scleroderma* may consist of repeated episodes of Raynaud s phenomenon These episodes may recur for many months before changes are noted in the texture of the skin Dysphagia due to esophageal involvement may also be an early manifestation Diffuse scleroderma is a systemic disease which may involve the pulmonary, cardiovascular, and other organ systems In *dermatomyositis* Raynaud s phenomenon again may be an early manifestation The cutaneous lesions tend to appear first on the eyelids and to have a purplish color There is great variability in the degree of skin and muscle involvement and the two are not always parallel in the same area In some cases the skin lesions predominate in others the picture is essentially that of a polymyositis Scleroderma like changes may appear in the skin in patients with both systemic lupus erythematosus and dermatomyositis A striking manifestation of all three diseases may be rapid loss of weight

Owing to the use of an increasing number of chemical substances in the treatment of disease, the problem of *allergic reactions to therapeutic agents* has become one of growing importance These reactions vary in seriousness from simple pyrexia to irreversible damage to the bone marrow with resulting thrombocytopenia bleeding and death The physician must be particularly alert to the possibility of drug allergy when a patient exhibits unexplained fever, a skin eruption, abnormalities of the peripheral blood or evidences of renal impairment Drug fevers following the initial exposure to a drug usually do not develop for 7 to 14 days but if there has been a previous exposure the reaction may occur within a few hours after re exposure The fever may be severe and swinging in type In addition to chills headache and abdominal symptoms, there may be urticaria angioneurotic edema joint manifestations, and occasionally central nervous system signs It may be difficult to obtain a history of drug ingestion but familiarity with the pattern of reaction to the various agents may give rise to suspicions which eventually lead to the correct diagnosis For instance when a patient enters the hospital with azotemia for which there is no clear cut explanation, it may be well to request a determination of the blood sulfonamide level Alertness to the earliest manifestations of a drug reaction may prevent the de

velopment of potentially fatal complications such as thrombocytopenia exfoliative dermatitis agranulocytosis and necrotizing angiitis

CONGENITAL DEFECTS

There are numerous congenital defects and developmental abnormalities which may never give rise to symptoms However others may on occasion serve as the basis of a serious disease process A few such lesions will be mentioned briefly to illustrate their potential importance A *Meckel s diverticulum* may become inflamed and give rise to symptoms simulating those of acute appendicitis or the islands of gastric tissue within the diverticulum may ulcerate and lead to repeated gastrointestinal hemorrhages *Diverticula of the duodenum* are seen in 2 to 3 per cent of all gastrointestinal x rays Only occasionally do they give rise to symptoms When they arise in the region of the ampulla of Vater and become inflamed or distended they may make pressure on the common bile duct with resulting biliary stasis formation of gallstones and intermittent jaundice There may also be pressure on the pancreatic duct A practical example of the importance of this lesion may be found in Chapter 7 on Jaundice The presence of a diverticulum may be overlooked unless this possibility is kept in mind when examining gastrointestinal x rays or when doing an exploratory procedure to determine the cause of a posthepatic obstructive jaundice

Illustrative Cases

I

(#594258 Admitted March 21 1952 Died April 5, 1952)

THIS 37 year old white housewife entered for surgical treatment of chronic rheumatic heart disease At age 12 she had a migratory polyarthritis lasting four months At age 25 following an uneventful pregnancy she was told she had a leaky heart At age 32 she first noted dyspnea on climbing stairs

In January 1952 she was referred for mitral valvulotomy During the preceding four years her dyspnea had become more severe She had coughed up blood on two occasions and had noted irregularity of her heart On examination the lungs were clear to percussion and auscultation The blood pressure was 120/80 pulse totally irregular A systolic thrill was palpable in the apical region The heart was enlarged to the left and there was prominence of the pulmonary conus P_2 was accentuated There was a rumbling diastolic murmur in the mitral area There was a loud blowing systolic murmur heard at the apex in the axilla and over the mid precordium It was loud in the pulmonic area and during expiration had a musical quality It disappeared with inspiration Electrocardiogram showed auricular fibrillation and marked right axis deviation Voided urine showed epithelial cells white cells and red cells as well as 1 plus albumin Hematocrit was 45 sedimentation rate 16 mm per hour leukocyte count 8 000 On fluoroscopic examination the right ventricle pulmonic conus and left atrium were all enlarged the left ventricle appeared normal There was deviation of the lower esophagus to the right and posteriorly by the enlarged left atrium There was accentuation of the bronchovascular markings bilaterally The impression was severe mitral stenosis with pulmonary congestion

In the middle of January the patient developed fever and malaise She had had influenza like infections once or twice a year which had always subsided after bed rest and penicillin therapy This attack was similar but she responded less promptly to penicillin than previously and continued to have an afternoon rise in temperature She had complained of pain in the lower back and occasional pains in her joints She was hospitalized for three weeks and given 900 000 units of penicillin and 1 gram of streptomycin daily She improved rapidly The urine cleared and the fever subsided She then returned for further study

PHYSICAL EXAMINATION on admission T 99 P 86 R 16 B P 110/80
The patient was poorly nourished but did not appear very ill No petechiae were noted There were suggestive clubbing of the fingers and spoon shaped nails The neck veins were distended The pupils were normal as was the funduscopic examination There was no lymph node enlargement The lungs were clear to percussion and auscultation The precordium was active The point of maximal impulse was in the 5th inter space 9 cm from the midline There was a systolic thrill over the whole precordium which on occasions was very intense There was auricular fibrillation A systolic shock was noted over the pulmonic region There was enlargement of the pulmonic conus and the heart was enlarged to the right An inconstant and changing rough harsh systolic murmur was heard over the whole chest and between the scapulas There was a low pitched diastolic murmur at the apex Peripheral pulsations were normal The abdomen was full there was shifting dullness and a fluid wave The liver extended 2 fingerbreadths below the costal margin The spleen was not enlarged Neurological examination was normal

COURSE IN THE HOSPITAL The temperature was never above 100 8 The finding which attracted most attention was the variable systolic sound over the anterior chest which was intermittent very loud and thought to represent some drastic alteration in the mechanics of the heart Some thought the sound was extracardiac in origin This harsh murmur varied greatly with respiration and was loudest when the patient was in the horizontal position Numerous blood cultures were taken all of which were sterile Tenderness was noted over the liver She continually com plained of abdominal distention On one occasion it was noted that with *deep inspiration the systolic murmur would entirely disappear for a few* beats and then would gradually become more intense with successive beats The liver grew larger She was given a mercurial diuretic following which she had palpitations and burning sensations throughout the body and be came very nervous Her respirations were shallow and rapid The skin was cool and moist although she complained of feeling hot The blood pressure and pulse became unobtainable During this period of profound peripheral circulatory collapse the patient was lucid mentally The extremities were cold and cyanotic The lungs were described as relatively clear It was thought that she probably had an anaphylactoid shock from the mercurial injection She died about 12 hours later

LABORATORY DATA Blood serologic test for syphilis negative hematocrit 45 icterus index 7 5 sedimentation rate 27 mm per hour Leukocyte count 7 400 with 3/ juvenile neutrophils and 82/ segmented neutrophils Blood nonprotein nitrogen 27 mg / total serum protein *6 8 gm / with 4 1 gm % albumin chloride 97 mEq Urine examination* showed no albumin occasional white cell red cell and granular cast Stool examination was normal Venous pressure was 230 mm of 5/ glucose Circulation time (Decholin) 40 seconds Vital capacity 2 5 liters Phenolsulfonphthalein excretion 65/ in 2 hours

DISCUSSION This patient had cardiac insufficiency which be came more severe during the last few months of life after a febrile

illness A peculiar and variable murmur developed and she died suddenly in peripheral circulatory collapse without pulmonary edema

At no time was there any elevation of the systemic blood pressure The evidence of enlargement of the right side of the heart, the accentuated pulmonic second sound, the prominence of the pulmonary conus and the dextrogram are indicative of hypertension in the pulmonary circulation There were no signs of diffuse pulmonary disease or of any primary disease of the pulmonary arterial tree so let us assume for the moment that the pulmonary hypertension was secondary in nature There was no evidence of pericardial disease nor do the facts point to a primary myocardial disease although acute rheumatic myocarditis cannot be excluded Two things suggest the possibility of congenital heart disease (1) the prominent systolic thrill and murmur and (2) the rather marked right axis deviation in the electrocardiogram Finally the presence of the apical diastolic murmur, the pulmonary hypertension the shape of the heart the story suggesting acute rheumatic fever, and the auricular fibrillation make it seem quite probable that this patient had mitral stenosis due to chronic rheumatic endocarditis If this were the basic diagnosis, we still must explain the febrile illness and the peculiar and variable systolic thrill and murmur

There was little fever after her admission to the hospital, so that if any infection were present it must have been in a relatively quiescent state The degree of fever was not inconsistent with that seen in congestive heart failure One possibility was that she had bacterial endocarditis There was no anemia no embolic phenomena, and no splenomegaly However, in view of the pre admission antibiotic therapy one cannot rule out this possibility The points against active rheumatic fever are the apparent response to antibiotic therapy and the absence of anemia and leukocytosis It does not seem possible to delineate further the cause of the febrile illness but I doubt if it was a factor of basic importance aside from its contribution to the progression of heart failure

The cause of the bizarre systolic thrill and murmur is of particular interest We should like to know first whether this sound was extracardiac in origin Extracardiac murmurs may be loud under certain circumstances, and may show great variation with the phases of respiration However two findings are strongly against an extracardiac origin of the murmur in this case (1) the intense thrill and (2) the escape phenomenon during maintained inspiration The conditions under which a peculiar systolic murmur and thrill may be en

countered have been reviewed previously (see Table 5) Such murmurs and thrills are usually attributable to a communication between the systemic and the pulmonic circulations or between the two sides of the heart There is little evidence in the present case to support any of these possibilities and none of them would explain the well documented intermittency of the thrill and murmur An interauricular septal defect which in the presence of mitral stenosis may be accompanied by a loud systolic murmur is the most likely possibility in this group but the murmurs would not be expected to exhibit such variability from day to day and with respiration

Two other possibilities exist which do not involve a shunt Occasionally a transventricular fibrous band presumably congenital is the only explanation for a systolic thrill and murmur found at autopsy These murmurs do not exhibit such great variation in intensity The final possibility is a movable intra auricular tumor mass either a myxoma or a thrombus With this type of lesion variability in the intensity of the murmur its occasional complete disappearance and changes in its quality depending upon posture and phase of respiration would be expected The final dramatic episode of forward failure might have resulted from sudden wedging of an intra auricular mass in the narrowed mitral orifice One might expect more evidence of pulmonary edema but this has not been a striking feature in cases of left auricular myxoma seen in this clinic The final obstruction was probably so complete that the signs of pulmonary edema did not have time to develop Since this patient has probable chronic rheumatic heart disease mitral stenosis and a large left auricle with auricular fibrillation I predict that a ball valve thrombus will be found in the left auricle

ANATOMICAL DIAGNOSIS (Autopsy No 23590) Chronic rheumatic heart disease with healing Aschoff bodies and myocardial scarring Massive endocardial scarring left auricle mitral and tricuspid valve Mitral stenosis and insufficiency Dilatation and hypertrophy right and left auricles and right ventricle Massive pedunculated mural thrombus left auricle Pulmonary arteriosclerosis with acute pulmonary arteritis Fresh pulmonary thrombi Chronic passive congestion lungs liver and pancreas Cardiac cirrhosis Pulmonary edema Lobular pneumonia Hemorrhagic ileitis Submucosal hemorrhages bladder and ureter Pyelitis cystica Primary tuberculous complex lung and hilar lymph node Medial cystic changes aorta and pulmonary artery Squamous metaplasia pancreas

The right auricle and ventricle were hypertrophied and dilated The tricuspid valve was fused had rolled margins and was obviously stenotic The left auricle was filled with laminated thrombus material and the entire thrombus mass was fresh enough to show well defined architecture

The lower margin of the thrombus had an accessory lobulated portion which acted as a ball valve in the mitral valve orifice The mitral valve showed extreme stenosis The chordae tendineae were short thick and rigid The lungs were heavy and contained edema fluid The liver showed extreme passive congestion

Healing Aschoff bodies were found on microscopic section of the myocardium There were also prominent perivascular scars and small arterial thickenings typical of healed rheumatic fever The thrombus compressed and impinged upon the ostia of at least two of the pulmonary veins Prominent interstitial scarring was seen in the alveolar walls in several sections It has been pointed out that this type of scarring is not seen in simple chronic passive congestion but depends upon stenosis of the pulmonary veins Sections of lung showed severe pulmonary arteriolosclerosis In some of these pulmonary arteries inflammatory cellular infiltration was seen in the wall as though an actual interstitial arteritis were present

SUMMARY This 37 year old housewife had rheumatic fever in childhood and heart disease was discovered after a pregnancy at age 25 At age 32 she developed overt cardiac insufficiency which grew progressively more severe Examination revealed heart failure with the clinical evidence of mitral stenosis A peculiar intermittent systolic thrill and murmur were present to the left of the sternum She died suddenly in peripheral circulatory collapse without evident pulmonary edema The conditions associated with circulatory findings of this type were reviewed and it was concluded that the patient had rheumatic heart disease with an intra auricular ball valve thrombus The autopsy revealed RHEUMATIC MITRAL AND TRICUSPID DISEASE, with evidence of recent activity of the infection There was a huge PEDUNCULATED THROMBUS IN THE LEFT AURICLE

II

(#540764 Admitted June 12 1950 Died July 4 1950)

THIS 39 year old white woman was admitted in a comatose state of 24 hours duration At age 17 she had developed arthritis involving her hands wrists feet and back The joint difficulty was active for 10 years leaving residual deformities Three years before her final illness she had a positive serologic test for syphilis and received penicillin The test reverted to a negative reaction

One month before admission while in church she suddenly became stiff all over and lost consciousness This episode lasted only a few moments afterward she felt tired but had no specific dysfunction There was no clonic seizure and no incontinence Five days prior to admission she had a similar episode No localized weakness followed but she did not feel well and stayed in bed She tended to repeat sentences from time to time The day before admission she suddenly became unconscious and had a generalized convulsion Following this she roused temporarily but soon lapsed again into an unresponsive state

PHYSICAL EXAMINATION on admission T 98 4 P 84 R 20 B P 110/70

The patient was underweight lay flaccid in bed and was unresponsive except to painful stimuli Her eyes moved about in an uncoordinated fashion There was no cyanosis The skin was pale and had a sallow appearance There were no petechiae There were ulnar deviation of the fingers and bulbous deformities of the metacarpophalangeal joints There was a dorsal kyphosis with limitation of motion of the spine The pupils reacted normally and the fundi showed no abnormalities The neck was supple There was no venous engorgement There was no adenopathy The breasts were normal The lungs were clear The point of maximal impulse was visible and palpable just inside the mid-clavicular line in the 5th inter space There was an apical systolic thrill The area of cardiac dullness was increased to the left M_1 was loud and snapping P was louder than A There was a harsh apical systolic murmur and also a blowing systolic murmur in the pulmonic area All peripheral pulsations were present and equal on the two sides No abnormalities were found on abdominal examination Pelvic and rectal examinations were negative There was no edema The cranial nerves all functioned well She moved all four extremities but movement was better on the left side than on the right The deep tendon reflexes were present and equal on the two sides hyperactive in the arms No abnormal reflexes were described

COURSE IN THE HOSPITAL. The temperature rose on the 6th day and

remained near 105 until death The pulse rate ranged from 110 to 140 After the results of the first blood and spinal fluid sugar were known she received intravenous glucose On June 15 she was a little more responsive but this improvement was not maintained On June 20 respiratory difficulty developed with retraction of the left chest on inspiration and absence of breath sounds An endotracheal tube was inserted and large amounts of purulent material were aspirated She was treated with penicillin The leukocyte count reached 32 600 Examination on June 22 revealed the larynx vocal cords and trachea to be edematous The following day the patient seemed more alert She moved the left side fairly freely and was noted to move her right leg On June 26 she seemed to comprehend what was said to her On July 1 her respirations were Cheyne Stokes in character She was sweating profusely July 2 she attempted to say a few words with some success She died apparently with respiratory obstruction on July 4

LABORATORY DATA The urine had a specific gravity of 1 020 and showed a trace of albumin an occasional red and white cell and a moderate number of hyaline and granular casts Hematocrit was 42 5 icterus index 7 5 sedimentation rate 2 mm per hour leukocyte count was 23 000 with 31% juvenile neutrophils 62% segmented neutrophils and 7% lymphocytes Blood chemical examinations on admission showed nonprotein nitrogen 33 mg % CO_2 combining power 25 8 mEq albumin 4 8 gm % and globulin 1 0 gm % On June 15 nonprotein nitrogen was 45 mg % sugar 124 mg % CO_2-combining power 24 2 mEq chloride 86 mEq sodium 124 2 mEq and potassium 3 8 mEq

Numerous blood cultures were sterile Urine culture showed no growth Serologic test for syphilis was positive—titer 1 unit Tuberculin test (OT 1 10 000) was negative Culture of tracheal aspirations showed a heavy growth of alpha streptococci a light growth of *Staphylococcus aureus* and a moderate growth of pneumococci

Lumbar puncture on June 13 revealed a spinal fluid pressure of 170 mm of water with no evidence of block 1 mononuclear cell per cu mm Pandy test negative Blood sugar was 12 mg % and cerebrospinal fluid sugar 12 mg % Cerebrospinal fluid chlorides were 122 2 mEq proteins 12 mg % Wassermann and colloidal mastic tests negative Spinal fluid culture showed no growth Second lumbar puncture on June 14 showed an initial pressure of 80 mm fluid was clear Cerebrospinal sugar was *130 mg % and blood sugar 182 mg %* Electrocardiogram on June 20 revealed sinus tachycardia T1 T2 and TV5 low Q T interval prolonged

On June 19 arteriogram was normal and the skull films showed no abnormalities Electroencephalogram revealed a focus of fast waves over the left temporal lobe area

On June 22 portable x ray of the chest showed a mottled infiltration through most of the left lung and in the upper half of the right lung The lungs appeared to be adequately expanded bilaterally There was no evidence of a pleural reaction

DISCUSSION The most prominent feature of this woman s illness was the *epilepsy* if this term is defined as the sudden and repeated

appearance of seizures in which convulsive movements or loss of con sciousness or both are the principal elements The seizure itself may be looked upon as a symptom analogous to a headache The list of the principal causes of seizures (Table 23) is a long one In many instances several factors may operate together to produce the seizure Idiopathic epilepsy may make its first appearance during the course of some unrelated illness particularly if fever is present

Table 23 Causes of Convulsions

I Generalized (with loss of consciousness) due to intrinsic cerebral involve ment (with or without increased intracranial pressure)

- A Infections and parasitic diseases
  - 1 Pyogenic abscess
  - 2 Meningitis
  - 3 Encephalitis
  - 4 Syphilis
  - 5 Tuberculosis
  - 6 Chronic arachnoiditis
  - 7 Cysticercosis
  - 8 Toxoplasmosis
  - 9 Cerebral malaria
- B Vascular lesions
  - 1 Hemorrhage
  - 2 Thrombosis
  - 3 Hemangioma
  - 4 Congenital aneurysm with subarachnoid hemorrhage
  - 5 Systemic lupus erythematosus
  - 6 Arteriosclerosis
  - 7 Subdural hematoma
  - 8 Ergotism
  - 9 Periarteritis nodosa
- C Tumors and cysts
  - 1 Congenital or acquired cysts
  - 2 Primary or secondary neoplasms
- D Degenerative diseases including demyelinizing diseases
- E Cerebral trauma
- F Functional changes
  - 1 Cerebral change in hydration anoxemia fever increased intra cranial pressure
    - a Water intoxication
    - b Angioneurotic edema
    - c Uremia
    - d Venous sinus thrombosis
    - e Eclampsia and toxemia of pregnancy
    - f Febrile convulsions in children
    - g Lead encephalopathy
    - h Hypertensive encephalopathy
    - i Heart block
    - j Severe anemia
    - k Dissecting aneurysm
    - l Hemorrhage with shock
    - m Vasovagal attacks
    - n Increased intracranial pressure

2 Abnormal composition of the blood
 a Hypocalcemia
 b Hypoglycemia—spontaneous and induced
 c Drug seizures (barbiturates picrotoxin caffeine benzedrine lead cocaine strychnine)
 d Hyperventilation
 e Oxygen intoxication
 f Carbon monoxide
 g Alcoholism

G Congenital maldevelopment
 1 Porencephaly
 2 Cerebral aplasia
 3 Cerebro macular degeneration

H Idiopathic epilepsy

II Local or Jacksonian

A Tumors

B Vascular disease

C Others

From the course of events in this case there is reason to believe that a local cerebral lesion was present There was no evidence of a space occupy ng mass with increase in intracranial pressure or dis placement of the arterial system The remaining types which remain for further consideration are some type of cerebral vascular dysfunc tion infection and degenerative disease

Now let us look at the causes of *coma* as shown in Table 24 When coma is a relatively early as well as a prominent manifestation of a disease process it may be the result of injury cerebral embolism or hemorrhage cerebral thrombosis either arterial or venous subarach noid hemorrhage or the acute effect of certain drugs It may also result from extremes of environmental temperature excessive loss of blood or acute cerebral anoxia such as accompanies vasovagal syn cope postural hypotension or heart block Many of these possibil ities can be readily ruled out in the present case It seems most likely that the cerebral manifestations were vascular in origin or possibly due to an infection If one assumes that the associated manifestations such as joint deformity cardiac murmur leukocytosis and positive serologic test for syphilis were part of the primary disease then the possible diagnoses are

(1) acute exacerbation of rheumatic fever
(2) bacterial endocarditis with cerebral emboli
(3) chronic rheumatic fever and carditis with mural thrombi and cerebral emboli,
(4) systemic lupus erythematosus,

Table 24 Causes of Coma (as an early or prominent feature of the illness)

I Intrinsic cerebral involvement
- A Space-occupying lesions
  - 1 Tumor
  - 2 Abscess
  - 3 Subdural hematoma
  - 4 Tuberculosis
  - 5 Gumma
  - 6 Intracerebral hematoma
  - 7 Aneurysm
- B Infections without abscess or tumor
  - 1 Meningitis
  - 2 Encephalitis
  - 3 Cerebral malaria
    - a Natural vector
    - b Human transfer
- C Vascular without tumor
  - 1 Hemorrhage
    - a Intracerebral
    - b Subarachnoid
  - 2 Thrombosis
    - a Arterial
    - b Venous
  - 3 Embolism
- D Trauma with
  - 1 Concussion
  - 2 Meningeal artery hemorrhage
  - 3 Fracture

II Functional changes
- A Metabolic and endocrine
  - 1 Uremia
  - 2 Cholemia
  - 3 Diabetic coma
  - 4 Addison s crisis
  - 5 Eclampsia
  - 6 Hypoglycemia (pituitary dys function hepatic disease pan creatic adenoma functional)
- B Oxygen deficiency
  - 1 Acute blood loss
  - 2 Vasovagal syncope
  - 3 Postural hypotension
  - 4 Carotid sinus hyperactivity
  - 5 Carbon monoxide poisoning
  - 6 Stokes Adams syncope
- C Drugs and chemicals
  - 1 Alcohol
  - 2 Hypnotics and opiates
  - 3 Lead
  - 4 Others
- D Physical disturbances
  - 1 Hypothermia
  - 2 Hyperthermia
  - 3 Pressure effects
- E Post epileptic
- F Hysterical
- G Terminal phase of severe infections carcinomatosis etc

If one accepts the diagnosis of an inactive arthritis having no relation to the final illness, then the additional possibilities to be considered are

(1) leukemia with cerebral thrombosis or hemorrhage
(2) a cerebral infection such as encephalitis or tuberculosis, or possibly a mycotic infection,
(3) myxoma of the left auricle with tumor emboli to cerebral vessels
(4) some disease leading to intermittent hypoglycemia,
(5) syphilitic vascular disease

Exacerbation of rheumatic fever at this patient s age with no evidence of acute arthritis or active carditis would be most unusual It would not provide a satisfactory explanation of cerebral manifestations of this type The course of the illness is unlike that of bacterial endocarditis There were no constitutional evidences of infection during the month before admission no evidences of emboli other than cerebral no anemia and no splenomegaly Many blood cultures were negative and there was no response to massive penicillin therapy One might make a plausible case for a diagnosis of systemic lupus The joint and cardiac lesions could be explained on this basis Involvement of cerebral vessels with attacks simulating epilepsy is encountered in patients with systemic lupus and cerebral hemorrhage with coma hemiplegia and death may occur The serologic test for syphilis might be a biologic false positive which occurs frequently in this disease It would be unusual for cerebral signs to be the only evidence of lupus and the leukocytosis would have to be attributed to some other factor such as cerebral tissue damage or pulmonary infection The latter was not noted at the time of admission when the leukocyte count was 23 000 However of the four possible diagnoses listed in the first group systemic lupus seems to account most satisfactorily for the facts as we have them

In reviewing the other group of possibilities leukemia seems entirely unlikely There was no enlargement of lymph nodes liver or spleen no anemia and no hemorrhagic tendency Although the high leukocyte count and the shift to the left of the granulocytes suggest infection it is difficult to see how this final illness could be primarily an infection of the central nervous system There was no evidence of encephalitis or meningitis There might have been an abscess secondary to an embolus or to some underlying pulmonary infection but one cannot make this diagnosis without evidence of a space occupying lesion The first clinical evidence of a myxoma of the left auricle may develop from small bits of tumor emboli entering the

systemic circulation These may lodge in the brain but they are usually small and do not lead to coma or death before there is evidence of cardiac dysfunction

The initial blood and spinal fluid sugars were recorded as 12 mg % but there was no symptomatic response to intravenous glucose Most patients with pancreatic adenomas of the islet type have a longer history of symptoms and they are overweight rather than thin as was this patient If one ignores the joint and heart trouble then the diagnosis of an islet tumor is the best one the assumption being that she had irreversible nervous system damage at the time of admission It seems unwise however to make this diagnosis when systemic lupus erythematosus offers a broader explanation of all the known facts

ANATOMICAL DIAGNOSIS (Autopsy No 22482) Pancreatic islet cell tumor in head of pancreas Spongy degeneration of occipital cortex Lobular pneumonia Acute splenic tumor Emaciation Central atrophy and mild fatty infiltration of liver Focal calcification of renal tubules Hyperplasia of femoral bone marrow

When the pancreas was examined an islet cell tumor was found There was apparent extension of the tumor cells through the fibrous capsule The occipital cortex showed a stratum of spongy alteration with loss of all recognizable neurons and increased vascularity of the immediately subjacent areas which may have been an effect of the hypoglycemia The pneumonia was extensive Microscopically the tumor was a typical islet cell adenoma with a thick fibrous capsule outside of which were small nests of tumor cells suggesting invasion and malignancy

SUMMARY This 39 year old white woman had transient attacks of unconsciousness one month and again five days prior to admission Twenty four hours before entry she had a generalized convulsion and remained comatose On examination she was unresponsive appeared underweight showed the deformities of a childhood arthritis had cardiomegaly and a systolic bruit The arm reflexes were hyperactive but the extremities were flaccid She lived for nine weeks and showed a slight increase in responsiveness and in her ability to move the extremities Her temperature remained high and she had signs of atelectasis and pneumonia Spinal fluid sugar and blood sugar were 12 mg % on the day after admission but she did not respond systemically to the intravenous administration of glucose There was albuminuria hematuria and cylindruria Because of the chronic arthritis and the evidence of cardiac disease systemic lupus erythematosus was considered to be the preferred diagnosis The failure of response to glucose was thought to be strong evidence against an islet cell tumor despite the low spinal fluid and blood sugar which was reported on only a single occasion This interpretation proved to be in error A PANCREATIC ADENOMA was found at autopsy Irreversible nervous system damage had apparently resulted from the low blood glucose level

III

(#210853 Admitted April 29 1952 Died April 30, 1952)

THIS 30 year old Negro female complained of cough dyspnea and pain in the chest of one week s duration She had had pneumonia in her early twenties Her first pregnancy was in 1947 when a hysterotomy was performed because of death of the fetus She was told that she had high blood pressure Subsequently she had three pregnancies the last in October 1951 and during each of these there were dyspnea orthopnea and edema of the ankles During the last pregnancy she was given digitalis and was told her heart was bad Between pregnancies she had no symptoms except occasional headaches Three years before admission she noted intolerance to heat definitely preferring cold weather She had increasing nervousness and fatigability and felt that her appetite had increased She denied weight loss

Two months before entry she developed a dry non productive cough accompanied by shortness of breath One month before admission she began to have feverishness at night and night sweats She became weaker and lost weight although her appetite remained good Her cough came in paroxysms and occasionally resulted in vomiting Five days before admission she developed a sharp pleuritic type of pain across the anterior upper chest bilaterally The next day she noted swelling of the ankles and on th following day was given a single injection of penicillin Her cough became productive of whitish sputum occasionally streaked with red Two days before entry orthopnea became pronounced and there were episodes of paroxysmal nocturnal dyspnea These symptoms grew progressively worse A second injection of penicillin was given the day before admission her temperature at that time being 101 She had been conscious of forceful heart action but had had no episodes suggesting paroxysmal tachycardia On examination in the Accident Room the temperature was 102 pulse 130 respirations 40 and blood pressure 100/60 She was cold and clammy and in view of her critical condition was sent immediately to the ward

PHYSICAL EXAMINATION on the ward T 102 P 116 R 32 BP 192/146

The patient appeared acutely ill and in severe respiratory distress without cyanosis There was evidence of loss of weight Her cough was productive of reddish tinged sputum The skin was smooth and the mucous membranes were pale The patient was sweating profusely There was pitting edema of the legs There were no abnormal eye signs There was attenuation of the retinal arterioles which showed areas of spasm and arterio-

venous compression The tongue was tremulous There was no lymph node enlargement The right lobe of the thyroid seemed a little full The neck veins were distended The neck was supple The thoracic excursions were shallow Over the right middle and lower lobes and the left lower lobe *there were increased tactile fremitus dullness tubular breathing* whispered pectoriloquy and fine and medium rales Fine moist rales were present over the posterior lung fields extending up to the mid scapular area A pleural friction rub was heard along the right sternal border The precor dium was active with the point of maximal impulse in the anterior axillary line in the 6th interspace The heart sounds were loud and forceful A presystolic gallop rhythm was noted but there were no murmurs The femoral pulsations were strong The liver extended 4 fingerbreadths below the costal margin and was tender

Course in the Hospital The patient continued to have a pulse rate around 120 and her temperature ranged from 101 to 102 with respiratory rate up to 42 Following an injection of chloramphenicol she complained of increasing shortness of breath Tourniquets were applied to the extremities but there was little improvement She became apprehen sive and cried out because of tightness in her chest and inability to breathe She developed overwhelming pulmonary edema with fluid issuing from her mouth and died

Laboratory Data Hematocrit 34 5 hemoglobin 10 gm icterus index 5 sedimentation rate 34 mm per hour Leukocyte count 14 000 with 7% juvenile neutrophils 80% segmented neutrophils 12% lymphocytes and 1% monocytes

Venous pressure 148 mm water circulation time 22 sec (Decholin) Blood serologic test for syphilis was negative Blood nonprotein nitrogen was 50 mg % sugar 96 mg % cholesterol 172 mg % CO_2-combining power 20 8 mEq sodium 140 mEq potassium 5 mEq chlorides 91 mEq

Sputum culture pneumococcus type XX mouse inoculated with spu tum died with a type XX pneumococcus infection Blood cultures were sterile

Electrocardiogram showed a rate of 120 P R interval 0 14 sec normal rhythm T waves isoelectric in leads 1 and 2 Q T interval at the upper limit of normal Record showed no abnormality other than the low T waves described

X ray examination of the lungs on April 29 showed diffuse mottling bilaterally The changes were more severe on the right side particularly at the right base which showed confluent density The heart was enlarged to the left The clouding of the right costophrenic sinus was thought to be due to fluid or consolidation The changes were compatible with pulmonary edema with or without a complicating bronchopneumonia

Discussion It would seem probable that this woman with a history of hypertension and symptoms of heart failure during preg nancies was suffering from a pulmonary infection which precipitated pulmonary edema and death This view is supported by the finding of pneumococci in the sputum However in an overwhelming pneu

moccal pneumonia the blood culture is usually positive The history also indicates that she had been ill longer than would be consistent with an acute pneumococcal infection alone

The friction rub heard along the right sternal border was pleural in origin *Pleurisy* is frequent in certain types of bacterial pneumonia In consideration of the various types of *pneumonitis* the first decision to be made is whether a pneumonia is primary in type or has occurred as part of a more general infection Of the various diseases complicated by pneumonitis tularemia seems a possibility in view of the duration of the illness and the x ray appearance of the lungs However a patient living in the city is certainly not likely to acquire tularemia in midwinter No organisms of significance other than pneumococci were cultured from the sputum and it seems probable that there was lobular pneumonia due to this organism However this was probably a late development and does not furnish an explanation for the entire course of events

Pulmonary infarction is difficult to rule out A large infarction in the presence of heart failure should have caused the icterus index to rise Pulmonary adenomatosis must be mentioned as a type of lesion which may simulate a pneumonitis but usually there is copious sputum which was not noted in this case Localized interstitial pulmonary fibrosis may also simulate pneumonitis but cyanosis should be conspicuous at this stage of the illness The only type of intrathoracic neoplasm that might be thought of seriously in a 30 year old Negro female is some type of lymphoma which seems a highly unlikely explanation for this picture The rapid progress and apparent virulence of the illness and the lack of evidence of lymphatic involvement seem to rule out sarcoidosis The combination of pneumonitis, pulmonary edema and leukocytosis suggests rheumatic fever However there was no history of this disease, nor were there any of the usual physical findings such as arthritis or myocarditis

The patient s race the length of the final illness and the character of the manifestations suggesting infection point strongly to the possibility of tuberculosis Acute tuberculous pneumonia may be associated with leukocytosis and shift to the left in the granulocytes In view of the location of the chest lesions, the leukocytosis, and the low level of circulating monocytic cells it seems unlikely that this was tuberculosis The association of the cough with increasing shortness of breath is more suggestive of cardiac insufficiency

The next problem to be considered is whether the patient had some underlying disease not directly related to the hypertension and not a

primary pulmonary disease The appearance of the x ray picture of the chest and the evidence suggesting infection make periarteritis nodosa a possibility She had had for two years symptoms suggestive of hyperthyroidism and it is well known that this disease may be closely simulated by a *pheochromocytoma In some cases the similarity* has led first to removal of the thyroid before the adrenal tumor was suspected Therefore these two possibilities must be kept in mind

The illness which began 6 days before death with pleurisy the signs of multilobar consolidation and the isolation of type XX pneumococcus from the sputum lead me to conclude that she had lobular pneumonia due to the pneumococcus

The hypertension which was unusually severe the story suggesting hyperthyroidism and the final episode of pulmonary edema makes pheochromocytoma the most probable diagnosis to account for the symptoms extending over a longer period This might also explain the rapid change in pressure from 100/60 in the Accident Room to 196/146 on the ward

ANATOMICAL DIAGNOSIS (Autopsy No 23637) History of intermittent hypertension and cardiac decompensation Pheochromocytoma adjacent to left adrenal Left ventricular hypertrophy Chronic passive congestion lungs and liver Hyaline arteriolosclerosis kidneys and pancreas *Early arteriolosclerotic nephritis Resolving pneumonia right lower lobe* with foci of organization Fresh thrombi in small pulmonary arteries Focal hemorrhages in lung Acute splenic tumor Acute pulmonary edema Hyperplasia femoral marrow Lobular hyperplasia breast

The left ventricle was dilated and hypertrophied The lungs were ex*tremely wet fluid exuding from the cut surfaces Attached to the right* adrenal was a well circumscribed large dark red tumor mass measuring 5 cm in diameter The other adrenal was normal

Microscopically the tumor was a typical pheochromocytoma There was chronic passive congestion Many hyaline arterioles were noted in the kidneys with involvement of the entering glomerular arterioles There were similar lesions in the pancreas The lungs showed a resolving pneumonia in the right lower lobe Many alveoli contained only macrophages but in others there was fibrin and a scattering of polymorphonuclear leukocytes There were some fresh thrombi in smaller pulmonary arteries and there were focal hemorrhages in the lungs There were scattered alveoli containing organized and organizing exudate These lesions could account for the symptoms beginning the week before death but none of them were old enough to explain the history of severe cough for two months One can only conclude that the patient s cough must have been the result of cardiac decompensation

SUMMARY This 30-year old Negro female had hypertension and evidence of heart failure during four pregnancies For three years she had had

signs suggesting hyperthyroidism Two months before death cough and progressive dyspnea appeared followed by persistent night sweats and weight loss Six days before entry she developed pleuritic pain and reddish sputum Examination revealed fluctuating blood pressure fever tachycardia profuse sweating edema retinal vascular disease signs of pulmonary consolidation cardiomegaly hepatomegaly anemia, leukocytosis and a type XX pneumococcus in the sputum The course of the illness suggested that an acute pneumonitis had precipitated severe heart failure in a woman with long standing hypertension The fluctuating blood pressure and the signs of hyperthyroidism suggested a PHEOCHROMOCYTOMA. The latter was found at autopsy together with a RESOLVING PNEUMONIA.

IV

(#297401 Admitted July 22 1943 Died October 16 1943)

THIS 73 year old white female complained of anemia fatigability and arthritis In 1924 the diagnosis of duodenal ulcer was made In 1940 she first suffered pain in the lower part of the back upon arising in the morning This was aggravated by movement but tended to disappear after she had been up and about for a while In 1941 her arthritis became worse she developed stiffness in other joints and noticed fatigability In 1942 the pains involved her hands hips and thighs During the winter of 1942 she injured her back Local back pain continued but x ray showed no evidence of fracture During the late months of 1942 she developed difficulty in walking and experienced a sensation of constriction about the hips In the spring of 1943 she noticed further lameness and became quite exhausted She was found to have albumin and casts in her urine hemoglobin of 58 per cent leukocyte count of 2400 with normal numbers of platelets There was marked variation in the size and shape of the red cells with many macrocytes and a rare nucleated red cell was seen She was placed on liver extract with no improvement Gastrointestinal x rays and barium enema were normal She developed painful swelling and inflammation of both legs with reddish splotches scattered over them The right tibia was painful and tender

PHYSICAL EXAMINATION on admission T 100 P 102 R 20 B P 125/75

The patient had lost weight There was pretibial edema an extensive purpuric eruption over the lower legs and scattered old purpuric spots over the thighs and upper extremities No hemorrhages or exudates were seen in the fundi The gums were pale The tongue was smooth generally with papillary atrophy at the edges The thyroid was palpable There was no lymph node enlargement There were fine to medium rales at both lung bases which persisted after cough No masses were palpated in the breasts The heart was enlarged to the left There was a low pitched blowing systolic murmur over the precordium There was distention of the neck veins The radial arteries were thickened The liver was felt at the costal margin No other organs or masses were palpable There were numerous Heberden s nodes There was no vibratory perception below the level of the iliac crests The deep and superficial reflexes were active and equal on the two sides

COURSE IN THE HOSPITAL There was no persistent elevation in temperature although occasionally it rose as high as 102 Her renal function

was poor and there was some elevation of the blood nonprotein nitrogen (61 mg %) She vomited frequently and required intravenous fluids X rays showed enlargement of the heart but no parenchymal changes in the lungs X rays of the bones showed hypertrophic arthritis of the cervical and lumbar vertebrae No metastases were noted Her hemoglobin was 46 % on admission with a leukocyte count of 2900 At one time she complained of small painful areas on the medial aspect of the right thigh which were thought to be thrombosed superficial varices Her memory was poor and at times she was disoriented No lesion was demonstrated by x ray in th stomach but the second and third portions of the duodenum were dilated No local deformity of the duodenal bulb was found She received transfusions for her anemia X rays taken on August 12 showed retention of barium in the stomach at the end of five hours There was a gradual rise in the nonprotein nitrogen the value reaching 81 mg % by August 16 Intensive treatment with liver extract resulted in no improvement A diagnosis of an intestinal obstruction partial third portion of the duodenum was made and an exploratory laparotomy was done on August 20

At operation the duodenum was normal Postoperatively the patient was frequently short of breath and perspired a great deal Fluid accumulated in the chest and repeated thoracenteses were carried out at times with removal of as much as 1000 ml The fluid was straw colored and had a specific gravity of 1 011 On September 7 it was noted that the right leg was swollen hot and painful The nonprotein nitrogen continued to rise being 113 mg % on September 9 She had a persistent leukopenia counts ranging between 2 000 and 5 000 On September 19 red circular lesions from 1–2 mm to several centimeters in diameter developed on the arms and hands and about the elbows She gradually became more confused and irrational and developed Cheyne Stokes respirations Prior to death the edema became generalized and profuse purpuric manifestatio s appeared

Laboratory Data Blood serologic test for syphilis was negative On July 22 1943 red blood cells numbered 2 1 million hemoglobin 7 0 gm hematocrit 19 4 icterus index normal sedimentation rate 17 mm per hour Leukocytes numbered 4 300 with 82% segmented neutrophils 3% eosinophils 10% lymphocytes and 5% monocytes Platelets were 136 000 bleeding time 2 min coagulation time 4 min moderate achromia no increase in reticulocytes mean corpuscular volume 93 mean corpuscular hemoglobin 33 mean corpuscular hemoglobin concentration 36 tourniquet test negative clot retraction normal

Urine on admission showed albumin 3 plus 8–10 white blood cells 8–10 red blood cells and 3–4 granular and hyaline casts per high power field Urine culture was sterile Phenolsulfonphthalein test of renal function showed 34% excretion in 2 hours The stool was poorly formed brown guaiac negative no ova or parasites were seen On July 26 nonprotein nitrogen was 61 mg % calcium 9 0 mg % phosphorus 4 1 mg % alkaline phosphatase activity 3 2 units On September 1 total serum protein was 4 8 gm % with albumin 2 7 gm % and globulin 2 1 gm %

Electrocardiogram on July 24 showed normal sinus rhythm T1 T2 and

T4F upright T3 isoelectric Left axis deviation There was a Q3 wave suggesting myocardial damage

DISCUSSION When this patient was first seen she was thought to have pernicious anemia There was no response to liver extract however and if one re examines the clinical picture closely it was not that of pernicious anemia Free hydrochloric acid is often not present in the gastric juice of patients at this age and there are numerous other conditions in which a macrocytic anemia may develop There was no hemolytic component to the anemia and young red cells were seen in the circulating blood Therefore we had best look for some type of disease which replaces enough functioning marrow to result in a picture of myelophthisic anemia

The presence of nitrogen retention might lead one to suspect that the anemia was secondary to impaired renal function The degree of anemia however was out of proportion to the degree of renal dysfunction as indicated by the nonprotein nitrogen level on admission The anemia of uremia is usually normocytic and rarely if ever does one find immature red cells in the circulating blood Moreover the leukocyte count is usually normal or slightly elevated in contrast to the leukopenia found here Also primary renal disease could not explain the other manifestations of this patient s illness

In the absence of loss of blood hemolysis or iron deficiency and in the light of the failure to respond to maturation factor anemia of this type with circulating normoblasts leukopenia and thrombocytopenia in an elderly woman is strongly suggestive of neoplasm with metastases to bone The absence of any evidence of lymphatic system involvement seems against Hodgkin s disease Moreover this diagnosis would not explain the renal failure Tumors of the breast lungs thyroid stomach and kidney may be associated with diffuse bony metastases with resulting myelophthisic anemia The breasts in this case were described as normal as were the lungs and thyroid Hypernephroma would produce a different type of renal picture and would not in itself account for the uremia If one considers the illness to have had its onset in 1940 then the back pain is not likely to have been due to metastases from any of these tumors

A macrocytic anemia may be associated with intestinal strictures which could conceivably have been the cause of the duodenal dilatation in this case However if one makes such a diagnosis other explanations must be found for the so-called arthritis and the kidney disease

If one looks now at the renal abnormality there are certain points

of interest Albuminuria was marked, the serum albumin was low and there was no hypertension There are three conditions which always come to mind with this picture (1) subacute bacterial endo carditis (2) amyloid nephrosis and (3) the myeloma kidney The last of these three diseases not infrequently presents itself with obscure anemia of the myelophthisic type and bone pain part cularly in the spine and hips often leads the patient first to the orthopedist When one considers this diagnosis further the events which took place seem to have a satisfactory explanation

In *multiple myeloma* the pain is often wandering and intermittent being referred most frequently to the back, as in this case Central nervous system symptoms secondary to the vertebral lesions are com mon and this might explain the loss of vibratory perception Gastro intestinal symptoms and petechial lesions are often seen, and intra vascular thrombosis may occur When the classic x ray picture of multiple myeloma is absent the blood changes may lead to the mis taken diagnosis of pernicious anemia Myeloma would also account for the nephritis without hypertension This disease is most common after the age of 50 years

It seems to me that multiple myeloma explains this complex picture so well that one need not seriously entertain any other possibilities Arthritis nephritis anemia and leukopenia might suggest systemic lupus erythematosus but the clinical course is not in any way typical

I believe that this patient had plasma cell myelomatosis The curi ous skin lesions although they were not described as being exclusively about the joints suggest the possibility of amyloid deposits of the type sometimes associated with multiple myeloma

ANATOMICAL DIAGNOSIS (Autopsy No 18594) Multiple myeloma myeloblastic History of macrocytic anemia Extramedullary blood forma tion in liver Hemosiderin in liver and spleen Scattered petechiae skin epicardium esophagus Arteriosclerosis aorta Arteriosclerotic nephritis Organizing fibrinous pericarditis Edema both legs Bilateral pleural effusion Slight pulmonary edema Dilatation right ventricle Acute gastritis Peripyloric adhesions

The liver was small and rusty in color as was the spleen The kidneys were reduced in size the surface was finely granular and the tissue pale On each side there were numerous tiny cysts which represented dilated tubules The cortex was thin and the striations difficult to see

Microscopic sections showed that the vertebra and ribs removed for routine autopsy sections were filled with myelomatous tumor The tumor cells almost completely replaced the vertebral marrow No normal marrow

or fat remained and the bony lamellae seemed rarefied There were dense masses of myeloblasts forming the tumor but here and there megakaryocytes and megaloblasts were also seen There was extramedullary blood formation in the liver and spleen and both organs contained much hemosiderin which was found chiefly in large macrophages The terminal uremia was evidently due in part to obstruction of the collecting tubules of the kidneys which were distended by large and dense protein casts possibly Bence Jones protein In addition there was extreme intrarenal arteriosclerosis with scarring and depletion of renal tissue which obviously added to the renal insufficiency Postoperative adhesions about the pylorus were found from organization of a localized subacute inflammation There was a widespread acute diffuse gastritis with many polymorphonuclear cells infiltrating the mucosa

SUMMARY This 73 year old white woman had an illness of 3 years duration characterized by pain and stiffness of the joints loss of weight fatigability a chronic purpuric eruption edema loss of vibratory sense anemia leukopenia albuminuria hematuria cylindruria and azotemia X rays of the bones showed evidence of arthritis The anemia failed to improve with liver extract and the renal insufficiency progressed rapidly although the blood pressure was normal The anemia on analysis seemed likely to be due to bone marrow replacement This together with the renal insufficiency the normal blood pressure and the bone pain led to the diagnosis of MULTIPLE MYELOMA This was confirmed at autopsy Extreme renal arteriosclerosis was also present

V

(#214421 Final Admission November 15, 1943
Died November 18, 1943)

THIS 63 year old white woman entered the hospital first on November 2 1940 complaining of excessive thirst excessive urination nervousness and insomnia These symptoms had begun 3 months previously with the sudden appearance of dryness of the mouth Before this she had been drinking large amounts of water and had voided large amounts of pale urine There was increasing loss of weight and weakness There was loss of the sense of smell for several years preceding the onset of the polydipsia For 10 years she had noticed on occasions palpitations dyspnea on exertion and swelling of the ankles but no orthopnea

SUMMARY OF FIRST ADMISSION *Physical Examination* T 99 6 P 80 R 20 B P 120/70 The patient was an obese woman in no distress The eyes were normally prominent The pupils reacted normally The tonsils were enlarged and scarred The lymph nodes at the angles of the jaw were palpable The thyroid was not enlarged The lungs were clear The heart was normal No masses or organs were palpable in the abdomen Neurological examination disclosed no abnormality

Course in the Hospital During the first week in the hospital her intake of fluid was 5 liters daily and the urine output was 2 to 4 liters Following treatment with Pitressin tannate the daily intake of water averaged 2 liters and the urinary output 1 to 1 5 liters She was discharged feeling well She was afebrile

Laboratory Data Blood serologic test for syphilis was negative hemoglobin 14 6 gm leukocyte count 6 840 with normal differential Specific gravity of the urine varied from 1 003 to 1 015 there was no sugar or albumin microscopically a few pus cells were seen Phenolsulfonphthalein test of kidney function showed 43 per cent excreted in 30 minutes 75 per cent in 2 hours Spinal fluid showed no abnormalities Tuberculin test (O T 1 10 000) slightly positive after 18 hours On roentgen examination heart and aorta were normal lungs clear skull normal

SUMMARY OF SECOND ADMISSION The patient entered for the second time on October 14 1943 About 2 weeks previously she had developed pain in the lower part of her back and had had fever and a chill She became constipated and had frequent nausea For about a month before the onset of these symptoms she had again been drinking water excessively and putting out large amounts of urine During the preceding year she had occasionally noted diplopia

Physical Examination T 99 2 P 94 R 28 B P 170/70 The patient was in no distress The skin was loose There was slight enlargement of the left pupil There was no enlargement of lymph nodes The lungs showed crackling rales at both bases The heart was a little enlarged the sounds were normal No abdominal organs or masses were felt There was edema of the ankles Neurological examination was normal

During a few days without treatment she drank 5–6 liters of fluid daily and had an output of 2–4 liters of urine After Pitressin the fluid intake was 4 liters daily and the output 2 5 liters Pus cells were found in the urine and cultures yielded colon bacilli She was treated with a sulfonamide and on discharge the cultures were sterile The temperature rose as high as 101 Blood pressure which on admission was 170/70 soon fell to normal

Laboratory Data Blood serologic test for syphilis was negative hemoglobin 11 7 gm leukocyte count 8 000 with normal differential Phenolsulfonphthalein test of kidney function showed 43 per cent excretion in 2 hours

Subsequent Course After discharge the patient again had fever malaise anorexia and progressive weakness These symptoms continued and she was readmitted on November 15 1943

PHYSICAL EXAMINATION on final admission T 101 2 P 78 R 22 B P 145/60

This time the patient appeared very ill The skin was loose and dry The eyes were normal There was no enlargement of lymph nodes There was dullness at both lung bases The heart was enlarged to the left There was a loud blowing systolic murmur over the precordium There was an occasional extrasystole Abdominal examination was normal except for tenderness at the left costovertebral angle Neurological examination revealed no abnormalities There was edema of the ankles

LABORATORY DATA The urine contained a trace of albumin a few pus cells and many granular casts Culture yielded alpha *Streptococcus faecalis* X rays showed *fluid in the left pleural cavity Five ml of serous* fluid mixed with blood obtained by thoracentesis contained 800 leukocytes per cu mm of which 50 per cent were polymorphonuclear cells A few large gram negative rods were seen in the smear

COURSE IN THE HOSPITAL The patient s temperature rose to 102 and before death reached 105 On the 4th day she was found comatose and deeply cyanotic with pin point pupils and Cheyne Stokes respiration Blood pressure was 170/90 An hour previously she had been in fairly good condition After this episode she was restless and confused Lumbar puncture showed normal fluid She became increasingly comatose and died

LABORATORY DATA Hemoglobin 11 gm hematocrit 35 leukocyte count 20 000 with a shift to the left nonprotein nitrogen 49 mg / total protein 5 56 gm / with albumin 2 81 gm /

Electrocardiogram on the day of death showed normal sinus rhythm left axis deviation T waves upright A premature contraction followed each sinus beat causing a bigeminal rhythm P waves preceded the extra systoles

DISCUSSION This is a case in which it seems difficult to find a single disease that will explain all of the events which took place The patient was apparently in good health until the onset of her polydipsia and polyuria However, there was a history of anosmia for several years previously, although she had no history of chronic

Table 25 Causes of Diabetes Insipidus

- I Defect of neurohypophysial system for production of antidiuretic hormone
  - A Congenital or primary type
  - B Acquired
    - 1 Trauma due to basilar fracture of skull
    - 2 Vascular lesions
      - a Thrombosis
      - b Hemorrhage
      - c Aneurysm
    - 3 Following acute infections
      - a Measles
      - b Mumps
      - c Scarlet fever
      - d Encephalitis
      - e Basilar meningitis
      - f Diphtheria
    - 4 With chronic infections
      - a Syphilis
      - b Tuberculosis
      - c Actinomycosis
    - 5 Neoplasms or cysts invading the diencephalo-pituitary region
      - a Primary
      - b Secondary
    - 6 Other diseases involving this region
      - a Sarcoidosis
      - b Eosinophilic granulomatosis
      - c Amyloidosis
      - d Leukemia
      - e Lymphoma
- II Refractoriness of renal tubules to antidiuretic hormone
  - A Congenital or hereditary
  - B Acquired secondary to renal and other urogenital diseases

rhinitis She had also had palpitation, slight exertional dyspnea and occasional edema of the ankles but on examination was found not to have peripheral arteriosclerosis significant cardiac murmurs, or evidence of chronic pulmonary disease

It seems reasonable to draw two conclusions at this point (1) The patient definitely had diabetes insipidus This means that there must have been some type of lesion in the hypothalamic system or in the posterior lobe of the pituitary The primary lesion causing this dis

turbance was not in the renal tubule since the functional disturbance could be corrected by the administration of Pitressin (2) If all of the manifestations were the result of a single disease then that disease must have been capable of involving a wide variety of tissues and structures so as to bring about dysfunction of the brain heart and kidneys

There are two ways in which one may attempt to solve this type of diagnostic problem (1) by referring to a list of various conditions known to cause *diabetes insipidus* (see Table 25) (2) by referring to a list of diseases which may cause widespread involvement with protean clinical manifestations

(a) Connective tissue disease { periarteritis nodosa / systemic lupus erythematosus
(b) Primary amyloidosis
(c) Leukemia
(d) Lymphoma
(e) Tuberculosis
(f) *Bacterial endocarditis*
(g) Hand Schuller Christian disease (eosinophilic granuloma)
(h) Sarcoidosis
(i) Metastatic neoplasms

It is of interest that in approaching the problem from these two points of view one finds several diseases on both lists Looking more closely at the causes of diabetes insipidus we may quickly discard some of them The idiopathic form is usually evident from infancy and is accompanied by no other manifestations There was no trauma in this case and the diabetes was not preceded by any acute infection Only in the terminal stages was there indication of any infectious process The blood serologic test for syphilis was negative and tuberculosis actinomycosis and other chronic infections seem unlikely No secondary malignant neoplasm would be expected to run such a protracted course No primary tumor or cyst would explain the renal and cardiac dysfunctions Leukemia would not ordinarily be present for such a long period of time without characteristic changes in the peripheral blood The remaining four diseases are not easy to rule out without more detailed analysis They are lymphoma sarcoidosis Hand Schüller Christian disease and primary amyloidosis

Now let us review the other list Some type of connective tissue

disease might be considered, but it would be most unusual to have diabetes insipidus as the cardinal manifestation The course is too long for metastatic neoplasm There might be some reason to suspect acute bacterial endocarditis as a terminal complication but subacute bacterial endocarditis could not account for the entire illness Thus we are again left with the same four major possibilities The next step is to see if any of the four could provide a satisfactory explanation for the entire illness

All four of these diseases may run a course benign enough to produce symptoms over the long period described Primary amyloidosis and lymphoma certainly are infrequent invaders of the diencephalo pituitary area In view of the fact that there is no positive evidence of either of these diseases let us turn our attention to the other two possibilities which are well known to be associated with diabetes insipidus Hand Schuller Christian disease is rare in adults but there is a generalized form in which brain lung skin and kidneys may be involved Sarcoidosis would not be expected to run its entire course without evidence at some time of lymph node involvement I can go no further now than to say that the diagnosis in this case may be either Hand Schuller Christian disease or sarcoidosis

It seems likely that some complicating infection was responsible for the terminal event There was a urinary tract infection which may have been caused by ureteral compression by a granuloma with resulting hydronephrosis The development of the murmur, the mild anemia and the final episode suggesting cerebral embolism would all be consistent with the development of a urinary tract infection, bacteremia and acute bacterial endocarditis If we assume that the patient had a cerebral embolus then there are at least three other possible sources (1) from the periphery through a patent foramen ovale (2) from left ventricular mural thrombi secondary to myocardial disease or (3) from thrombi on an arteriosclerotic aortic plaque Of these various possibilities I would favor the diagnosis of acute bacterial endocarditis even though the one blood culture was negative

In conclusion it seems to me that the whole picture can best be explained on the basis of eosinophilic granuloma or sarcoidosis with cardiac pulmonary renal and cerebral involvement ureteral obstruction urinary tract infection, bacteremia and acute bacterial endocarditis with cerebral emboli

ANATOMICAL DIAGNOSIS (Autopsy No 18637) Hand Schuller Christian disease involving skin renal pelves with extension into pyramids and

cortices mesentery omentum spleen peripancreatic fat diaphragm aorta lungs pleura epicardial fat mediastinum bone marrow hypophysial stalk History of diabetes insipidus Mural thrombi aorta Thrombi in splenic artery and vein Massive infarction of spleen Thrombi in renal arteries Infarcts in left kidney Thrombi in mesenteric and hepatic arteries Central necrosis in liver Melanosis coli Colloid adenomas of thyroid Cholesterosis of gallbladder Caseous encapsulated tuberculous lesion in lung

The spleen was enlarged and adherent to the diaphragm Its lower half formed a cavity which was evidently a liquefied infarct In the upper half there were infarcts varying in color In the left kidney there was a yellowish red area 2 cm in diameter suggesting an infarct at the apex of which there was an occluded blood vessel The calyces immediately beneath this area were dilated The right kidney was uniformly pale The adipose tissue about the pelvis was hard and mottled on both sides and the pelvis and upper portion of the ureter were narrowed and the calyces were dilated The aorta was extremely sclerotic and many of the plaques were soft and yellow with bits of thrombus material on the surface There was a thrombus in the superior mesenteric artery

On examination of the microscopic sections the bone marrow was largely replaced by foam cells and by macrophages which did not contain lipoid Eosinophils were not conspicuous Some of the fat laden cells were enormous with large hyperchromatic nuclei In the sites mentioned in the diagnosis there were similar accumulations of lipoid laden and non-lipoid containing macrophages but in many of the sites there remained only scars with nondescript mononuclear cells In these scars one found scattered cells of the characteristic type but often they were scarce The scars clearly represented areas in which the normal tissue had been replaced by the abnormal macrophages and then these in turn had been replaced by scars Thus all stages of this process could be seen The stalk of the hypophysis was destroyed The structures of the hypothalamus showed no invasion by the specific cells It was thought that thrombi in the various arteries represented emboli from the aortic thrombi The diabetes insipidus was explained by the involvement of the hypophysial stalk

Summary This 63 year old white woman developed polydipsia and polyuria 3 years before death with loss of weight and weariness She was obese but showed no other abnormalities Her fluid intake was 5 liters daily and the urine output was 2–4 liters A diagnosis of diabetes insipidus was made and she was regulated with Pitressin tannate Six weeks before death she developed back pain fever nausea polydipsia and polyuria *Examination showed a low grade fever loss of weight* pulmonary basilar rales slight cardiomegaly ankle edema and anisocoria She was again regulated on Pitressin and discharged The fever continued and she was readmitted four days before death There was dullness at the lung bases cardiomegaly a loud systolic murmur tenderness in the left costovertebral angle ankle edema albuminuria pyuria cylindruria and a positive urine culture for *Streptococcus faecalis* Fluid containing many leukocytes and

gram negative bacilli was aspirated from the left pleural cavity There was a mild anemia leukocytosis and slight azotemia The response to Pitressin indicated that the DIABETES INSIPIDUS was due to a lesion of the neurohypophysial system and the evidence of widespread tissue involvement suggested EOSINOPHILIC GRANULOMA or sarcoidosis Autopsy revealed widespread eosinophilic granulomas with typical lesions in all stages of development The stalk of the hypophysis had been destroyed by granulomatous tissue There were many intra arterial thrombi and emboli

VI

(#324859 Admitted June 22 1944 Died August 1 1944)

THIS 48 year old housewife entered complaining of anemia During the late summer of 1940 she had developed grippe with aching joints elevation of temperature and a yellowish tinge to her skin The joint symptoms disappeared in a few days but she continued to run a low grade fever Her hemoglobin was 28 per cent Studies disclosed no cause She improved slowly with iron and liver therapy After three months she resumed her usual activities although her hemoglobin never rose above 58 per cent In December 1943 she developed bronchopneumonia Her hemoglobin again fell to very low levels It gradually rose between the time of that episode and admission to the hospital She continued to have slight elevations in temperature She lost no weight

PHYSICAL EXAMINATION on admission T 99 8 P 100 R 20 B P 104/70

The patient was well developed obese and did not appear acutely ill Her skin was soft pale and had a yellowish appearance There was no lymph node enlargement No jaundice or cyanosis was noted The thyroid felt normal The lungs were clear No cardiac impulse was felt The left border of dullness was 12 cm from the midline in the 5th interspace There was an apical systolic murmur radiating into the left axilla Diastole was clear The liver edge was 2 fingerbreadths below the costal margin The spleen could be felt There were no abnormalities on neurological examination

COURSE IN THE HOSPITAL During the first week the patient s temperature varied between 99 2 and 100 2 A sternal puncture was attempted but no marrow could be obtained Two days later the temperature rose gradually reaching 103 She developed signs of consolidation at the left lung base with evidence of fluid in the pleural cavity These signs cleared over the next few days during which time a pericardial friction rub was heard She was given salicylates and her temperature returned toward normal but later rose again reaching 107 before death Lymph nodes became palpable in the left axillary and inguinal areas The abdomen became distended and ascites was present

LABORATORY DATA Blood serologic test for syphilis was negative Red blood count was 3 75 million hemoglobin 7 3 gm hematocrit 26 3 icterus index 6 sedimentation rate 2 mm per hour mean corpuscular volume 70 mean corpuscular hemoglobin 17 mean corpuscular hemo-

globin concentration 28 Leukocyte count 4 200 with 74% polymorphonuclear cells 1% eosinophils 21% lymphocytes and 4% monocytes Smear showed achromia with slight anisocytosis and moderate poikilocytosis Platelet count was 220 000 reticulocytes 1 8% nucleated red blood cells 1 to 100 white blood cells Fragility test normal Prothrombin time on July 22 21 5 sec (normal control 14 sec) Stools were negative for blood and parasites Blood chemical examinations were all normal The non protein nitrogen rose to 75 mg % the day before death when the blood salicylate level was high Bromsulfalein test showed 5% retention in 30 minutes Blood cultures showed no growth aerobically or anaerobically

Electrocardiogram on July 6 1944 showed normal sinus rhythm sinus tachycardia T waves were all low and diphasic probably due to digitalis

X ray examination of the chest on June 22 showed the heart enlarged to the left The lungs were clear there was a calcified node at the root of the left lung Flat plate of the abdomen on June 28 showed enlargement of liver and spleen Kidney shadows were normal On July 31 the size of the cardiac silhouette and the width of the mediastinal shadow had decreased

DISCUSSION The outstanding feature of this case was the *chronic anemia* which was present for four years This anemia persisted despite iron and liver therapy It was microcytic and hypochromic in type there was no evidence that it was due to loss of blood or hemolysis There was no papillary atrophy of the tongue and no neurological manifestations There was enlargement of the liver and spleen without enlargement of the superficial lymph nodes, and there was a low grade fever There was no loss of weight and there was a remarkably good adjustment to the anemia Some observers have for practical purposes divided chronic anemias into two major groups

(1) Anemias in which some abnormality in the peripheral blood helps immediately in making a diagnosis Under this heading is pernicious anemia leukemia parasitic anemia with eosinophilia parasitic anemia with parasites in the blood Obviously none of these was present in this case

(2) Anemias with a non specific or negative blood picture This group may be subdivided into those in which an obvious cause is detectable such as chronic nephritis chronic infection, drug intoxication, etc and those in which there is no obvious cause and in which circumstances suggest that the disease is unusual

Obviously this case falls into the second group and the possibilities to be considered are those diseases which may suppress bone marrow function or cause a reduction in the amount of functioning bone

marrow which produce no diagnostic hematological picture and which are accompanied by no symptoms or signs which make the cause of the anemia obvious This seems a rather complex approach but with the steps so far taken most of the diseases likely to cause a severe anemia have been eliminated as possibilities Of those remain ing the diagnosis apparently lies among the following

(a) Some type of chronic obscure infection such as tuberculosis or histoplasmosis
(b) Rheumatic fever with the subsequent development of subacute bacterial endocarditis
(c) Connective tissue disease of another clinical type such as systemic lupus erythematosus
(d) Hernia at the esophageal hiatus or some other cause of obscure blood loss
(e) Hodgkin s disease or lymphosarcoma
(f) Myelophthisic anemia due possibly to
    (1) Metastatic carcinoma of bone marrow
    (2) Myelosclerosis

It would be unusual to see such severe and prolonged anemia as the outstanding feature of tuberculosis and the cutaneous tuberculin reaction was negative Pulmonary calcification in a patient with a negative tuberculin reaction suggests histoplasmosis and fever splenomegaly and anemia may all be encountered in this disease However one would not expect the active phase of histoplasmosis to run such a prolonged course The severity of the anemia in the absence of other characteristic manifestations is against this being any type of connective tissue disease Both Hodgkin s disease and lymphosarcoma may produce anemia with hepatomegaly splenomeg aly and leukopenia and without thrombocytopenia or lymph node enlargement However the lack of symptoms and the failure to lose weight during a four year illness are not usually encountered in lymphomas The same may be said for any type of carcinoma which may involve the bone marrow The clinical course is somewhat more suggestive of some type of fibrosis or sclerosis of the marrow with the development of extramedullary blood formation in the liver and spleen However the eventual appearance of enlarged lymph nodes the hepatomegaly and splenomegaly and the ascites during the final illness weighs the scales in favor of a lymphoma of some type

With this diagnosis it becomes difficult to explain the terminal por tion of the patient s life without bringing in other factors However

we know that she had bronchopneumonia previously and possibly had it again A reaction to sulfadiazine or salicylates might well have been the cause of the terminal delirium hyperpyrexia, and renal insufficiency It is also possible that infection or hemorrhage or both in the mediastinum or pericardial sac followed the attempted sternal puncture

ANATOMICAL DIAGNOSIS (Autopsy No 19066) History of anemia Lymphosarcoma with generalized enlargement of lymph nodes and wide spread infiltration of organs Compression of portal vein by enlarged lymph nodes Ascites Organizing fibrino hemorrhagic pericarditis Enlarged spleen Malposition of gallbladder

The epicardium was covered by a fairly thick layer of blood stained fibrin that showed organization In the posterior part of the left lower lobe just below its apex there was a calcified tuberculous focus Hilar lymph nodes contained partially calcified tuberculous lesions The liver was large and swollen About the head of the pancreas there were numerous enlarged lymph nodes which appeared to be more or less continuous due to infiltrating tumor The head of the pancreas was surrounded and infiltrated by tumor The spleen was enlarged Its pulp was grayish red and firm The kidneys were moderately enlarged and swollen The cortical markings were obscured and even the pyramidal striations were hazy The mesenteric lymph nodes were enlarged and on section were seen to be surrounded by strands of gray tissue that looked like tumor All of the intra abdominal lymph nodes were enlarged and infiltrated with tumor

On microscopic study the architecture of the lymph nodes was obliterated by masses of lymphocytes which also infiltrated the tissue about the nodes The liver showed periportal infiltration with the same cells and there were frequently clumps of lymphocytes in the sinusoids related to similar infiltrations in the substance of the liver In this respect the condition differed from leukemia in which the sinusoids everywhere contain an excess of cells There were lymphocytic infiltrations in the kidneys uterus and elsewhere including the bone marrow The pathological picture was interpreted as that of lymphosarcoma rather than leukemia but it may be noted that it is unusual to find in lymphosarcoma such large numbers of small diffuse infiltrations The portal vein was surrounded and compressed by enlarged lymph nodes which were doubtless responsible for the ascites The pericardium showed an organizing fibrinous and hemorrhagic exudate This might have been caused by the trauma of the attempted sternal puncture

SUMMARY This 48 year old housewife had an unexplained anemia with low grade fever four years before death Six months before bronchopneumonia developed followed by return of severe anemia and continued pyrexia She was febrile appeared pale and had slight hepatomegaly and splenomegaly She remained febrile Following attempted sternal puncture her temperature rose signs of pulmonary consolidation appeared and a

pericardial friction rub was heard Later lymph nodes were palpated in the axillary and inguinal areas and ascites developed There was a severe anemia and a slight tendency to leukopenia Occasional nucleated red cells were seen The central features were the chronic anemia which did not respond to liver or iron therapy hepatomegaly and splenomegaly There was no evidence of blood loss or hemolysis The diagnosis finally chosen was miliary LYMPHOSARCOMA The diagnosis was confirmed by autopsy

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systole The peripheral pulses were all palpable The abdomen was soft and no organs or masses were palpated There was no edema On neuro logical examination of the cranial nerves the visual fields were found full to white and colored objects but there was enlargement of the blind spots Optic discs showed papilledema and numerous hemorrhages and exudates were scattered about the discs and through the macular and central areas The right pupil measured 5 5 mm the left 4 5 mm both reacted sluggishly There was a bilateral sixth nerve weakness There was third nerve weaknes on the right side An obvious right facial weakness peripheral in type was present as well as a right fifth nerve palsy with depression of the corneal reflex and a diminished response to pinprick and light touch Motor system The patient was unable to sit up stand or walk She could not voluntarily move her body or limbs from the lower trunk downward The leg muscles were reduced in bulk and were flaccid There was moder ately good strength in the arms The deep tendon reflexes were absent throughout as were the abdominal reflexes Sensory system All forms of cutaneous sensation were perceived over all parts of the body There was no sharp sensory level but awareness of sensation increased gradually as testing progressed up the legs and then more abruptly at the level of T12 Position sense was absent in the feet but present at the knees

COURSE IN THE HOSPITAL Because of the evidence of increased in tracranial pressure a ventricular tap was done The dura was tense The ventricle was entered at a depth of about 3 cm on the left slightly deeper on the right 25 to 30 ml of clear colorless fluid was obtained under increased pressure The patient had four generalized seizures in the next 24 hours She appeared cyanotic respirations were irregular pulse was weak and fast Blood pressure was 200/140 She had a low grade fever Subsequent ventricular taps revealed dark bloody fluid The patient re mained comatose and died on the fourth hospital day

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin 14 5 gm Leukocyte count 9 700 Urine was cloudy specific gravity 1 012 albumin 1 plus microscopic examination showed epithelial cells bacteria and crystals

Ventricular puncture Pressure was elevated 14 mg % protein Wasser mann reaction negative colloidal mastic test 0 Pandy negative Total cells 800 white cells 134 with 122 mononuclears of varying sizes

Chemical examination of the blood on July 2 showed nonprotein nitro gen 60 mg / chlorides 95 mEq On July 3 nonprotein nitrogen was 86 mg % sodium 141 mEq potassium 7 mEq chloride 87 mEq

DISCUSSION Three groups of manifestations characterized this illness (1) *paralysis of the lower extremities with pleocytosis in the spinal fluid followed by an elevation in spinal fluid protein* (2) *increased intracranial pressure with multiple cranial nerve paralyses and severe papilledema* and (3) *a marked degree of arterial hypertension* It would seem important in the analysis of this problem to list the possible causes of paraplegia and of multiple neuronitis which may involve

predominantly the lower extremities to review the causes of severe hypertension and finally to consider the causes of marked increase in intracranial pressure Was the original paraplegia part of the same disease which later caused the increase in intracranial pressure or were there two separate conditions? Was the hypertension secondary to the increased intracranial pressure or was it a manifestation of an underlying vascular disease? Was the renal insufficiency secondary to the nervous system disorder and the operative procedure, or was it an integral part of the original illness?

The term *paraplegia* signifies partial or complete bilateral paralysis of the legs This may be due to changes in the brain the spinal cord the peripheral nerves or the muscles In children it may be caused by congenital defects such as porencephaly or it may result from birth injuries meningocele congenital or acquired hydrocephalus superior longitudinal sinus thrombosis meningitis or encephalitis The lower motor neuron type may be due to poliomyelitis to peroneal muscular atrophy or to peripheral neuritis resulting from diphtheria or other causes In adults the rapid development of a paraplegia in a patient who has previously been well brings to mind a different set of causes The lower motor neuron type may be due to peripheral neuronitis so called acute infectious polyneuritis poliomyelitis, tumor of the cauda equina compression of the lumbar enlargement of the cord as a result of disease of the vertebrae or a pelvic tumor involving the lumbosacral plexus In the present case it is difficult to tell from the data at hand whether we are dealing with a cord lesion with a sensory level or with a lower motor neuron lesion of extensive degree The sensory changes as described perhaps favor the latter as does the complete absence of reflexes The initial pain however, had a root distribution and a questionable sensory level was made out Among paraplegias of the upper motor neuron type one must consider transverse myelitis which may be primary and of unknown etiology or it may be due to compression of the cord resulting from disease of the vertebrae from injury from an aneurysm from an infection such as actinomycosis or tuberculosis from an hour glass tumor or perhaps from a retroperitoneal tumor This type of lesion also may be seen during the course of disseminated sclerosis amyotrophic lateral sclerosis syringomyelia meningitis hemorrhage cerebellar tumor or abscess bilateral cerebral softening or hemorrhage and encephalitis as well as bilateral tumor metastases in the central nervous system

I find it impossible to decide whether this was primarily a cord

lesion or a polyneuronitis so we had best consider the possibilities in both categories The most likely of these are primary transverse myelitis compression of the cord due either to an infection such as tuberculosis or to a tumor chronic arachnoiditis localized meningitis acute infectious polyneuronitis or a diffuse polyarteritis which may have affected predominantly the nerves to the lower extremities as is sometimes the case Among the tumors we have to consider a primary extramedullary tumor a cauda equina tumor and retroperitoneal sarcoma

Now let us turn for a moment to the terminal phase of the illness in which there was evidence of increased intracranial pressure *Papilledema* is much more probable than papillitis if the disc elevation is over 3 diopters if there are numerous radial hemorrhages if the veins are clearly distended and venous pulsations absent if visual acuity is preserved until late in the course of the illness and if the only scotoma is an enlarged blind spot It would seem most likely that this girl did have papilledema Many conditions may lead to *increased intracranial pressure* with papilledema A tumor or some other space occupying lesion may interfere with the circulation of cerebrospinal fluid Intracranial sinus thrombosis may decrease the pathways of absorption and lead to papilledema The cerebral manifestations in hypertensive encephalopathy may be identical with those seen in epilepsy brain tumor cerebral hemorrhage or thrombosis or encephalitis Papilledema may also accompany infections of the central nervous system including meningitis It may appear during the course of acute infectious polyneuronitis and it may be present in neuromyelitis optica in which there is the picture of increased intracranial pressure and also a paraplegia of the upper motor neuron type However the papilledema is usually slight and headache and vomiting are rarely present Both of these symptoms were prominent features in this patient

Let us now look at the *causes of hypertension* The blood pressure may rise when there is a sudden increase in intracranial pressure but sustained elevations in intracranial pressure do not usually have this effect to any significant degree With most intracranial tumors even when papilledema is present there is no systemic hypertension unless there is a sudden change in the volume of intracranial contents as occurred in this case Hypertension may occur in the course of periarteritis nodosa It may occur with other types of vascular disease or vascular anomalies of the kidneys It may result from involvement of the kidney parenchyma as in glomerulonephritis pyelonephritis

and congenital polycystic disease or from retroperitoneal masses causing pressure on the kidneys In the present case the urinary findings were of the type seen with circumscribed involvement of the renal parenchyma rather than with diffuse involvement In other words if this patient had significant renal disease it is more likely to have been pyelonephritis or congenital polycystic disease than glomerulonephritis Another possible cause of the hypertension would be a pheochromocytoma

Several possibilities emerge from the review of the causes of the major disorders which were seen in this patient (1) She may have had infectious polyneuronitis or transverse myelitis which involved bladder function and led to an ascending infection of the urinary tract with subsequent development of pyelonephritis This may in turn have resulted in the development of hypertension and finally severe hypertensive encephalopathy, perhaps associated with intracranial hemorrhage and an intracranial hematoma (2) The paraplegia may have been associated with extradural involvement of the cord or nerve roots by a tumor even though no change in dynamics was reported This conceivably may have been due to a lymphosarcoma or a retroperitoneal sarcoma of the reticulum cell variety and the cells found in the spinal cord may have been tumor cells Retroperitoneal sarcomas and reticulum cell sarcomas may involve the brain and the final episode may have been due to metastatic lesions in the central nervous system which caused blocking of the ventricular system and led to the cranial nerve dysfunctions In this event the hypertension might have been due in part to the increased intracranial pressure and in part to pyelonephritis developing as a result of a cord bladder (3) The whole picture might be explained on the basis of polyarteritis the original lesions producing an extensive polyneuritis with later involvement of the central nervous system vessels and finally leading to the development of severe hypertension This type of progress is not infrequently seen in cases of periarteritis nodosa

With regard to *metastatic brain tumors* there are certain facts of interest They constitute 20 to 50 per cent of all brain tumors Thirty per cent of them originate from bronchogenic tumors, and 5 per cent from breast tumors Sarcomas are more prone than carcinomas to metastasize to the brain For instance 50 per cent of all melanomas metastasize intracranially Usually the symptoms are of sudden onset and brief duration This is important as these cases are apt to be confused with vascular disorders Headache is said to be out of pro

portion to the degree of increased pressure and signs of meningeal irritation are common There may be carcinomatous invasion of the meninges and subarachnoid space leading to headache confusion delirium meningeal signs and signs of multiple cranial and spinal nerve involvement In the present case there is strong evidence of a space occupying lesion in the central nervous system The operative findings are more in keeping with this than with diffuse cerebral edema My final conclusion is that this patient had lymphosarcoma of the miliary type

ANATOMICAL DIAGNOSIS (Autopsy No 23747) Lymphosarcoma involving abdominal lymph nodes pancreas stomach intestines ovaries kidneys heart meninges psoas muscle brain and spinal cord and cerebral and spinal nerves Acute necrosis of the adenohypophysis Marked papilledema History of flaccid paraplegia increased intracranial pressure and cranial nerve palsies Bilateral occipital trephine openings

There was a diffusely infiltrating white tumor nodule with central hemorrhage in the right auricular wall The liver appeared swollen but distinct lobulation was present The lobulation of the pancreas was obscured by firm white infiltrating tumor The mesentery contained confluent masses of hemorrhagic mottled tumor Small tumor nodules bulged beneath the mucosa of the jejunum replacing its wall In one adrenal there were two small white tumor nodules The right kidney was tremendously enlarged On the surface of the kidneys there were confluent pale nodules with hemorrhagic centers The right ovary was tremendously enlarged and was replaced by lobulated hemorrhagic tumor There was diffuse hemorrhagic discoloration along the surface of the spinal cord and flat tumor nodules were visible beneath the arachnoid The subarachnoid hemorrhage and tumor extended into the cauda equina The nerve roots showed bulbous hemorrhagic swelling obviously due to tumor The most interesting feature was the widespread infiltration in the meninges of the brain and spinal cord The tumor cells infiltrated cerebral and spinal nerves and penetrated along the blood vessels into the substance of the central nervous system as sheaths of cells about the vessels There were no parenchymal nodules of tumor in the central nervous system This state of the meninges and nerves made quite understandable the neurologic manifestations that the patient showed clinically The bone marrow in the sections available showed little alteration There was acute necrosis of the hypophysis

SUMMARY This 18 year old school girl developed pain in the thoracic and lumbar spine followed by paralysis of the legs A mononuclear pleocytosis with increase in protein was noted A few months later headaches attacks of numbness of the face diplopia with bilateral sixth nerve palsy vomiting and soreness in the legs appeared Examination revealed fever slight proptosis hypertension increased intracranial pressure with papilledema attenuation of retinal arterioles multiple cranial nerve palsies and a flaccid paraplegia with absent reflexes and diminished sensation

extending up to the level of T12 After ventricular decompression she had four convulsions and died in a coma with progressive azotemia It was difficult to decide whether she had multiple neuronitis or a paraplegia due to involvement of the cord but the evidence of nervous system change was widespread No diagnosis could be made with certainty but tumor of some type seemed likely and because of the extensive and bizarre central nervous system involvement LYMPHOSARCOMA of the miliary type was suggested This proved to be correct

VIII

(#136976 Final admission November 28 1943
Died December 5 1943)

THIS 38 year old Negro housewife complained of nose bleeds and generalized tenderness In March 1925 she had had multiple ulcers over the vulvae a left inguinal bubo acute salpingitis and a positive Wassermann reaction Two months later she had florid secondary syphilis papular in type with condylomas and general adenopathy After six injections of an arsenical she developed exfoliative dermatitis which healed after eight weeks In November 1926 she was given one injection of an arsenical and developed her second attack of arsenical dermatitis which was mild She had had twelve children five of them were living and well

One week before admission she had a shaking chill and felt feverish The following day she bled from the mouth nose and vagina She developed generalized tenderness of the skin and could not be moved without crying out in pain Her epistaxis persisted She was delirious for five days before admission and was presumably anuric for two days

PHYSICAL EXAMINATION on admission T 102 2 P 108 R 10 B P 84/50

The patient was acutely ill but not dyspneic or cyanotic No fresh eruption or petechiae were seen There was slight icterus She was dehydrated and disoriented Herpes of the lips was noted The pupils were pin point and reacted sluggishly There was clotted blood in the nose There was no lymph node enlargement No masses were found in the breasts The lungs were clear The heart was normal The abdomen was soft There was tenderness on percussion over the liver The knee kicks were hypoactive There was dark clotted blood in the vagina The outlet was relaxed and there was a cystocele and rectocele The cervix was enlarged and softened and there was brownish mucoid material coming from the os The uterus was not enlarged but there was thickening at the base of the left broad ligament It was the opinion of the gynecological consultant that the uterine bleeding was due to a generalized infection and not to local disease

COURSE IN THE HOSPITAL. The patient ran an irregular fever with temperature ranging up to 101 6 She grew more disoriented and continued to bleed from her nose uterus and gastrointestinal tract She was catheterized daily with removal of 300-600 ml of urine Three days after admission she became comatose and the liver edge was palpable The icterus grew more marked and cervical rigidity was noted prior to death

LABORATORY DATA Blood serologic test for syphilis was negative On December 1 red blood cell count was 1 84 million hemoglobin 6 gm, hematocrit 21 sedimentation rate 16 mm per hour Leukocyte count was 22 000 with 30% juvenile neutrophils 68% segmented neutrophils 1% eosinophils and 1% lymphocytes Mean corpuscular volume was 114 mean corpuscular hemoglobin 33 mean corpuscular hemoglobin concentration 29 Platelets appeared adequate in smear There was no sickling There was moderate aniso and poikilocytosis Prothrombin activity was normal

The stools showed clots of blood Urine had a specific gravity of 1 010 albumin 3 plus sugar 0 red blood cells 4-5 and white blood cells 20-30 per high power field with no casts Trace of bile On November 29 blood nonprotein nitrogen was 200 mg %, total serum protein 5 88 gm % with albumin 2 94 gm % bilirubin 7 7 mg % total 6 direct phosphorus 11 4 mg % alkaline phosphatase activity 13 3 Bodansky units cephalin flocculation 4 plus Sulfanilamide blood level was 0 3 mg % Blood culture showed no growth

No leptospira were seen in catheterized urine specimen or in blood smear on darkfield examinations Guinea pig inoculated with urine did not develop leptospirosis On December 1, darkfield of blood smear showed two long motile organisms one of which had hooked ends Most observers thought that these were leptospira On December 2 spinal fluid was clear Pandy negative with 460 red cells per cu mm, and an occasional neutrophil No leptospira appeared on darkfield examination On December 3 agglutination test for Weil s disease was negative

Electrocardiogram on November 29 showed normal sinus rhythm normal axis T1 T2 and T3 upright P R interval 0 20 sec

DISCUSSION Certain evidence is missing which might be of importance for the correct analysis of this problem One might ask whether the anemia was simply due to acute blood loss or whether in view of the jaundice it was hemolytic in nature No hemoglobinemia or hemoglobinuria was described but she was seen too late to expect this No tests were done for urobilinogen in the urine or stools and no reticulocyte counts were recorded The leukocyte picture was quite compatible with a hemolytic anemia In the absence of precise information we shall have to assume that the anemia was due to a combination of hemolysis and blood loss

In view of the findings and the rapid progress of the illness, several diseases will be considered

Acute infectious hepatitis may run a fatal course in less than a week The severity of the azotemia in this patient would be unusual The leukocytosis might be accounted for by sudden extensive liver necrosis However the jaundice was not unusually severe

The course of the illness does not seem consistent with any type

of primary renal disease The primary disease would have to be one which was capable of causing both liver and kidney dysfunction This brings to mind lower nephron nephrosis which may follow a hemolytic process Acute hemolytic anemia resulting from the devel opment of autohemolysins may run a course suggestive of an acute febrile illness Restlessness and irritability are common Hemorrhagic manifestations however are unusual and although signs of urinary retention may appear they are seldom so severe The anemia may be macrocytic Other primary blood dyscrasias such as chronic hemolytic anemia or acute leukemia need not be discussed in any detail as there are obvious strong points against them

It seems unlikely that this was an allergic reaction to sulfonamides but it is possible One would have to assume that the patient devel oped an acute infection took sulfonamide and had a fulminating allergic reaction within a few hours since the hemorrhagic phenomena came very quickly

The final possibility is that this was some sort of fulminating infec tion Weil s disease was obviously the choice of those who saw her but although there is much to support this possibility there are also some very strong arguments against it The sudden onset jaundice myalgic pains epistaxis signs of meningeal irritation azotemia and leukocytosis are all recognized manifestations of this disease One would not expect however such severe hemorrhagic phenomena or such marked azotemia so early in the course of the illness It was thought that leptospira were seen in the blood during the second week when they may occasionally be present However if this were Weil s disease in such a fulminating form with such marked renal involvement the urine should have easily killed the susceptible guinea pig I discount the suspected organisms in the blood as they are usually not present there after the first week of the disease The absence of agglutinins at this stage is not of great significance

Suppose for a moment that this woman who had had twelve preg nancies thought that she was pregnant again and was discouraged enough at the prospect to do something about it She might have attempted this by taking large doses of quinine or some other proto plasmic poison I have seen a case of quinine poisoning which showed all the manifestations that this patient displayed It is more likely however she would have attempted abortion by mechanical means This might have led to an infection The early and continued vaginal bleeding and the brownish mucoid discharge together with the soft patulous cervix are compatible with this possibility Such infections

may be due to *Clostridium welchii* hemolytic streptococcus *Streptococcus viridans* or *Staphylococcus aureus* and the bacteremia is often accompanied by a severe hemolytic anemia Localized abscesses may develop in the liver and kidneys, and together with the shock and hemolysis might adequately account for the magnitude of change in renal function seen here The absence of organisms on blood culture might suggest that *Cl welchii* was the major offender, and that the severe systemic manifestations were due to its potent toxin

ANATOMICAL DIAGNOSIS (Autopsy No 18669) Puerperal infection (mixed flora) Involuting pregnant uterus, gangrenous endometritis and cervicitis purulent salpingitis right hyperplasia of breasts jaundice acute splenic tumor cloudy swelling of organs History of uremia Interstitial nephritis focal syphilitic nephritis chronic cystitis and pyelitis Pulmonary edema and fresh lobular pneumonia diphtheritic epiglottis calcified hilar node right

The spleen was slightly enlarged The lining of the enlarged uterus was necrotic irregular masses of dead tissue projecting into the lumen The left ovary contained a yellow corpus luteum with a white center Extending from this ovary there was a long round mass 1 5 cm in diameter which contained several lumina in which there were thrombi

On microscopic section it was obvious that there had been extreme infection of the puerperal uterus There was much inflammation with many bacteria The right tube showed the same condition but the left was not involved The kidneys showed an interstitial nephritis Most of the cells were mononuclear but there were large numbers of eosinophils among them In two areas there were depressed scars rich in lymphocytes containing tubules that were dilated and filled with amorphous debris containing cholesterol crystals These had the appearance of old focal syphilitic nephritis There was widespread pulmonary edema and fresh lobular pneumonia The central portions of all liver lobules were disorganized Many of the cells had pyknotic nuclei and contained fat This appeared to be a fresh central necrosis of the liver

SUMMARY This 38 year old Negro housewife had had 12 pregnancies, with five children living and well In 1925 she developed syphilis and had arsenical dermatitis on two occasions One week before admission she had a chill developed fever followed by epistaxis vaginal bleeding generalized tenderness and oliguria Noted on examination were disorientation dehydration herpes icterus hepatic tenderness enlargement of the cervix uteri and a brownish uterine discharge She continued to bleed became more icteric developed cervical rigidity and became comatose There were anemia leukocytosis with shift to the left and severe azotemia with albuminuria The central features were evidence of infection severe hepatic and renal involvement and hemolytic anemia A primary hemolytic anemia or one due to drug administration seemed unlikely and the final choice lay between leptospirosis and INFECTED ABORTION The latter was found at autopsy

IX

(#142517 Admitted December 6 1953
Laparotomy December 15 1953 Died December 24 1953)

THIS 42 year old Negro man complained of severe pain in the abdomen of two weeks duration In 1941 he had been hospitalized with multiple stab wounds of the right and left chest An x ray revealed no pneumothorax or hemothorax although there was subcutaneous emphysema on the left The patient averaged one quart of wine daily He had had 4 or 5 episodes of the shakes In 1948 he was admitted with a diagnosis of lobar pneumonia In 1952 he was admitted with a story that for 3 weeks he had had pleuritic pain with fever chills and cough He had signs of consolidation over the left lower lobe and a pleuropericardial friction rub A small amount of fluid accumulated in the left pleural cavity A type XVIII pneumococcus was isolated In 1943 he had burning on urination which soon cleared

About one year before admission he noted the sudden onset of sharp pains in the periumbilical region which radiated into the left flank The acute pain lasted for a few moments and then became dull and crampy in character This pain occurred at intervals during the two weeks prior to admission being aggravated by ingestion of food He felt feverish and developed a constant headache He felt some tightness in the precordial region unrelated to exertion

PHYSICAL EXAMINATION on admission T 101 4 P 72 R 20 B P 110/70

The patient appeared chronically ill and cachectic The mucous membranes were pale No skeletal abnormalities were noted Examination of the eyes revealed no abnormalities The teeth were in poor condition A few axillary nodes were palpated There was dullness to percussion at the right base with some suppression of breath sounds A few fine rales were heard at the end of inspiration at both lung bases Respiratory movements were equal bilaterally and the diaphragm descended well Percussion showed the left border of cardiac dullness to be in the mid-clavicular line The sounds were of normal quality There was a grade 2 apical systolic murmur An extracardiac sound along the left sternal border was thought to be a pericardial friction rub The peripheral pulses were palpable and symmetrical The abdomen was distended and tympanitic He winced from abdominal pain when he moved The bowel sounds were good There was moderate rebound tenderness especially in the left lower quadrant but no real rigidity Tenderness was most marked in the left mid abdominal

region No masses were palpable The liver was percussed 1 fingerbreadth below the costal margin The genitalia were normal Rectal examination showed no abnormalities Neurological examination was negative

COURSE IN THE HOSPITAL The patient ran an irregular fever with temperature ranging from 99 6 to 102 6° Most conspicuous were the variable findings in the abdomen It became distended from time to time and during these periods the patient complained of a great deal of pain and tenderness and there was exquisite rebound tenderness At other times there was only mild tenderness localized to the left side of the abdomen These changes varied from day to day In general he continued to have severe abdominal pain which was described as cramplike in character He vomited occasionally Bowel movements were normal in form were clay colored and were negative for occult blood Tests for urobilinogen in the feces were positive The leukocyte count remained between 13 000 and 17 000 On December 15 a definite mass was felt in the left upper quadrant, over which there was dullness to percussion This mass was tender to palpation and there was questionable fluctuation Bowel and urinary function remained unchanged Exploratory laparotomy was decided on

LABORATORY DATA Blood serologic test for syphilis was negative Hematocrit 29 icterus index less than 5 One differential leukocyte count showed 4% juvenile neutrophils, 72% segmented neutrophils 2% eosinophils 19% lymphocytes and 3% monocytes Urine had a specific gravity of 1 004 to 1 010 no sugar or albumin occasional white cells in most specimens no red cells or casts Gastric juice showed no free acid prior to the administration of histamine Serum nonprotein nitrogen was 17 mg % total serum protein 6 7 gm % with 3 3 gm % albumin Cephalin flocculation and thymol turbidity normal Total bilirubin normal Bacteriological studies of gastric washings showed no acid fast organisms Tuberculin test with second strength PPD was positive after 24 hours X ray examination of the abdomen demonstrated gas within the small bowel With barium enema no lesions were seen below the hepatic flexure The ascending colon filled poorly and nearby there were several loops of gas filled small bowel These changes suggested an obstructive process The possibility of neoplastic disease of the ascending colon was considered although the changes on the films were not sufficiently definitive to establish this diagnosis It was thought possible that the changes observed were due to an extrinsic lesion as well as to a collection of peritoneal adhesions Examination of the stomach revealed no lesion but there was some dilatation of the duodenum This finding was possibly related to an obstructive process lower in the abdomen

DISCUSSION (The results of the operation were unknown to the discusser) This patient s chief complaint was of severe pain in his abdomen which radiated into the left flank The abdominal findings seemed to vary greatly from day to day Eventually a mass could be felt protruding beneath the left costal margin This led to the decision

for laparotomy There were a number of preoperative findings which may be of importance

This patient had a history of a stab wound although there is no evidence that it penetrated beneath the thoracic wall There was also a history of what were apparently recurrent attacks of pneumonia On looking at the x ray there are additional changes (1) some suggestion that there was a mass along the lesser curvature of the stomach which may have been pushing the stomach to the left and (2) in at least one film small deposits of calcium in an area near the head of the pancreas Obviously a great number of diagnostic possibilities arise In the area of the pain and in the region in which the mass was felt a number of organs exist the stomach and duodenum the colon the spleen the kidney the left lobe of the liver the pancreas retroperitoneal tissues the adrenal and the omentum These structures might be the site of an infection an ulcerative lesion a perforation a vascular lesion a neoplastic lesion or a cyst It would seem to me that there is no indication that this patient had any significant degree of intestinal obstruction as the basic lesion and tumor of the bowel or volvulus with obstruction would seem unlikely Moreover we have little reason to consider seriously such possibilities as a cyst of the omentum or of the omphalomesenteric duct or such vascular lesions as a dissecting aneurysm It also seems unlikely from the description of the findings that this lesion arose in the retroperitoneal area and it would seem unnecessary to discuss such possibilities as retroperitoneal sarcoma psoas abscess primary tumor of the kidney or primary tuberculosis of the kidney The stomach itself appeared to be normal in the x ray pictures although it may have been shifted by some extrinsic mass The pain did not resemble that due to a gastric ulcer and there was no evidence of such a lesion in the x ray Gastric carcinoma would hardly have extended over such a long period of time without more obvious changes in the x rays It would seem however that this patient still might have had a perforation of a viscus with a walled off abscess in the left upper quadrant It would be unusual to encounter a subphrenic abscess without more localized tenderness and without some elevation of the diaphragm Such reasoning also rules out a diaphragmatic hernia either on a congenital basis or secondary to a rent in the diaphragm following the stabbing In view of the normal position of the bowel in the x rays and the location of the pain he almost certainly did not have appendicitis Furthermore the repeated negative examinations as far as the urine was concerned the location of the mass and the

type of x ray findings all would seem to rule out a perinephric abscess The normal barium enema at least as far up as the hepatic flexure would seem to indicate that this man did not have a carcinoma of that portion of the colon as the primary lesion This would also follow from the absence of any change in bowel habits and the absence of blood in the stools

The remaining possibilities which must receive more serious consideration are duodenal ulcer with perforation and an abscess in the left upper quadrant diverticulitis with perforation and an abscess in the left upper quadrant carcinoma of the tail of the pancreas with possible invasion and thrombosis of the splenic vein tuberculous peritonitis and chronic pancreatitis with activity at the time of admission and with the development of a pancreatic cyst The barium enema showed no diverticula and perforation of a diverticulum with the formation of a mass in the left upper quadrant would be quite unusual If this were a carcinoma of the tail of the pancreas one would expect ascites rather than the development of a mass in the left upper quadrant since invasion of the peritoneum is common with this type of tumor The severity and duration of the pain and the nature of the mass would be against a diagnosis of simple tuberculous peritonitis although it is difficult to exclude this possibility The location of pain and the development of a mass in the left upper quadrant make it difficult to rule out a duodenal ulcer with perforation and the development of a localized abscess However, the type of pain and the absence of x ray evidence of an ulcer do not support this possibility This leaves us with the possibility that the patient had chronic pancreatitis and an inflammatory mass due to escape of pancreatic enzymes into the surrounding tissues The character and location of the pain as well as its radiation would seem to fit well with this possibility The patient had lost considerable weight which is quite characteristic of chronic pancreatic disease he was also a chronic alcoholic which provides the right setting for this disease Whether it is significant or not he had abdominal distention off and on during his stay in the hospital and on several occasions was noted to have clay colored stools in the absence of jaundice indicating that there was poor absorption of fat This might conceivably be attributed to pancreatic insufficiency The suggestion that there was displacement of the stomach might also be compatible with such a lesion

The mass that was felt might have been omentum brought up into the area by an inflammatory reaction about the pancreas There was

vidence in the x ray pictures of calcium deposits in the region of the
ead of the pancreas On the basis of the evidence it seems most
robable that this patient had chronic pancreatitis with an episode
f acute activity Bacterial infection with pancreatic abscesses may
ave been superimposed on the chronic disease leading to a fatal
utcome

NATOMICAL DIAGNOSIS (Autopsy No 24796) Extreme scarring of
ancreas dilated ducts with inspissated exudate partially calcified sub
cute pancreatitis severe (gram negative rods) Organizing abscess tail
f pancreas History of subphrenic abscess left with surgical drainage
paracolon escherichii) generalized and organizing fibrinopurulent perito
itis small organizing (? septic) infarcts left adrenal Tubular degeneration
f adrenals Acute ileitis with perforating ulcer Acute splenic tumor
Central atrophy liver Pulmonary edema pulmonary emboli right upper
obes Pleural adhesions pericardial adhesions

At operation an abscess cavity was found between the under surface of
he liver and the stomach Superficial examination of the stomach revealed
o evidence of an ulcer so the abscess was drained and the wound cleaned

In the microscopic sections from autopsy material there was no meta
lasia of the pancreatic ducts There appeared to be obstruction by
ispissated and calcified material and there was dense scarring of the
ancreas The cause of the superimposed infection was not clear but
here was an intense subacute pancreatitis and in the tail of the pancreas
here was an organizing abscess which may have been the source of the
bscess found by the surgeon and of the generalized peritonitis which
vas present The lesion of the ileum probably resulted from intubation

UMMARY This 42 year old Negro man who was a chronic alcoholic
ne year before death had sudden severe upper abdominal pain which
asted for 2 days In the interval before admission he had recurring attacks
f a similar type and lost 40 pounds in weight Examination at the time of
dmission revealed fever cachexia a pericardial friction rub and a dis
ended tender abdomen He continued to have fever pain and leukocytosis
ntestinal x ray studies revealed gas filled loops of bowel suggesting obstruc
ion and there was thought to be an extrinsic lesion displacing the stomach
ater examination of the films revealed tiny flecks of calcium in the region
f the pancreas He continued to have fever pain and leukocytosis A
alpable mass developed in the left upper quadrant and an exploratory
peration was performed The nature and location of the pain the history
f alcoholism the cachexia the absence of localizing abdominal signs
ntil the mass appeared and the probable calcification in the pancreas
d to the diagnosis of CHRONIC CALCAREOUS PANCREATITIS with a
uperimposed bacterial infection This diagnosis was confirmed at autopsy

X

(#65893 Admitted November 4 1935 Died December 8 1935)

THIS 59 year old Negro woman complained of vomiting and diarrhea In 1933 a diagnosis of hypertrophic arthritis had been made Four weeks before admission she began to feel bloated and after a dose of calomel she had nausea and vomiting The following day there was abdominal pain particularly on the right side and she continued to vomit Soon after there was diarrhea and the stools were black and tarry There was pain with defecation and the stools seemed to grow progressively smaller in size During the month s illness she vomited from time to time ate little and continued to pass tarry stools On the day before admission there was vaginal bleeding

PHYSICAL EXAMINATION on admission T 100 4 P 98 R 24 BP 136/74

The patient was an obese woman complaining of severe abdominal pain She was drowsy and confused The pupils were equal regular reacted actively eye movements were normally performed The fundi showed a moderate degree of arteriosclerosis Many teeth were missing and those remaining were carious There was no enlargement of the superficial lymph nodes The thyroid was not felt The lungs were clear except for a number of fine rales heard at the base of the right lung The heart was not enlarged At the apex there was a systolic murmur The pulse was regular equal at the two wrists There was a moderate degree of generalized arteriosclerosis The abdominal wall was tremendously thickened and flabby There was general abdominal tenderness In the right lower quadrant there was a mass which could not be definitely outlined The liver and spleen were not enlarged There was edema of the lower extremities The neurological examination was normal The pelvic examination (by gynecological consultant) revealed the following the fundus of the uterus was three or four times larger than normal and slightly irregular There was tenderness on both sides of the pelvis with thickening in the broad ligaments The rectal examination disclosed definite infiltration in both uterosacral ligaments and along the left what appeared to be a chain of small glands could be felt The gynecologist s diagnosis was probable adenocarcinoma of the fundus of the uterus with extension along the ligament

COURSE IN THE HOSPITAL The patient grew progressively worse She complained constantly of abdominal pain She vomited persistently There was edema of both legs being more marked on the right Signs

seeming to indicate intestinal obstruction grew more pronounced Vomiting became more and more severe and daily enemas became less effectual The patient became progressively weaker and increasingly anemic until death occurred 34 days after admission The temperature varied from 98 6 to 102 4 The pulse varied from 70 to 120

LABORATORY DATA Hemoglobin on admission was 83/ red blood cells 3 8 million and leukocyte count 8 000 with normal differential On December 2 hemoglobin was 40/ red blood cells 2 6 million and leuko cytes 6 000 Blood serologic test for syphilis was negative

On November 11 nonprotein nitrogen was 25 mg / serum proteins 6 1 gm % chlorides 93 2 mEq On November 25 nonprotein nitrogen was 30 mg % plasma proteins 5 75 gm % chlorides 100 8 mEq CO_2 com bining power 58 4 vol %

Specific gravity of the urine ranged between 1 006 and 1 015 There was no sugar At first there was no albumin later a heavy trace and both white and red blood cells Stools were dark tarry black in color Guaiac test and microscopic examination were both negative

Fasting gastric contents showed no free hydrochloric acid After hista mine free hydrochloric acid was 13% combined acid 10 5 /

Fluoroscopic examination on November 6 showed no definite evidence of a lesion in the stomach or duodenum but interpretation was difficult because of the patient s obesity A constant filling defect in the base of the duodenal cap was suggestive of ulcer On fluoroscopic examination on November 8 the sigmoid colon was displaced medially suggesting the presence of an extrinsic mass in the pelvis There was also a pressure defect on the wall of the cecum Plates of the abdomen showed the sigmoid portion of the colon rising well out of the pelvis suggesting the possibility of a pelvic mass outside of the colon and numerous diverticula in the descending colon There was no evidence of neoplasm

Fluoroscopic examination on November 11 showed normal stomach and duodenum The cecum was irregular in outline suggesting the presence of an organic lesion Fluoroscopic examination on November 18 showed the same filling defect previously noted in the cecum indicating the pres ence of an organic lesion in the cecum

On November 14 1935 the patient was examined under gas anesthesia A piece of cervix was removed and the uterus was dilated and curetted The pathologist reported chronic cervicitis The curettings provided in sufficient tissue for diagnosis

DISCUSSION This was an acute illness which had many of the aspects of an infection Duration from day of onset to day of death was almost two months The most important objective findings were the mass felt in the right lower quadrant on rectal examination under anesthesia and the fever and progressive anemia Vomiting per sisted and there was abdominal distention suggesting intestinal ob struction I would think it important that on the second day of her illness after ingestion of the calomel there was severe and persistent

pain in the right lower quadrant of the abdomen and later a mass in that area was the most consistent objective finding

The normal contents of the right iliac fossa are of course the cecum the appendix and the lower coils of ileum Abnormalities which may involve these structures fall roughly under three major headings (1) infections including appendicitis actinomycosis ileo cecal tuberculosis tuberculosis of mesenteric glands and regional ileitis (2) neoplasms of various sorts including carcinoma of the cecum sarcoma of the intestine and carcinoma of the appendix and (3) certain other abnormalities such as intussusception or other mechanical disorders which might give rise to obstruction Under certain conditions other structures may be present in this area including the liver the gallbladder the right kidney and pelvic organs as well as cysts and tumors of the right ovary and uterine fibroids or neoplasm Tumor masses in this area also may originate from structures composing the posterior wall of the fossa including enlarged glands from either infection or tumor of the external iliac group iliopsoas abscess aneurysm of one of the local arteries or tumors arising from bone There is also some indication from the x ray examination that there may have been a mass on the left side of the abdomen with displacement of the sigmoid Here one would have to consider the possibility of infections and of tumors including diverticulitis carcinoma of the colon a kidney tumor or abscess cysts or tumors of the left ovary iliopsoas abscess or any of the other lesions noted above

It would seem unlikely that this was primarily a neoplasm in view of the acuteness of onset of symptoms and the rapid progress of the disease Carcinoma of the colon or of the cecum would not produce such rapidly progressive anemia with persistently negative guaiac test on the feces The gynecological examination gave no indication that this mass originated in the ovary and the signs were not those of the ordinary type of adenocarcinoma of the uterus There is nothing to suggest that the mass was attached to bone The immobility of the mass and the entire course of events certainly did not suggest chronic intussusception from a tumor of the lumen of the bowel particularly the lower ileum Intestinal or lymph node tuberculosis is probably the third most common cause however of a mass in this area In view of the age of the patient and the course of the illness it would seem unlikely that it was due to tuberculosis Difficult to distinguish from ileocecal tuberculosis is cancer of the cecum which has already been discussed Actinomycosis is an infection which characteristically may

begin in the cecal area It may extend out of the gut itself and by direct invasion may involve contiguous structures leading to the formation of large inflammatory masses However the acuteness of the manifestations here the severity of the vomiting the rapidly progressive anemia and death within the period of eight weeks all would seem incompatible with actinomycosis The possibility of multiple masses raises the question of retroperitoneal sarcoma or Hodgkin s disease There was no enlargement of superficial lymph nodes and this together with the manner of onset and violence of the intestinal manifestations would seem inconsistent with a diagnosis of lymphoma or retroperitoneal sarcoma Sarcoma of the intestine itself is quite rare usually involves the lower ileum or cecum and is more common in children than in adults Clinically it may resemble ileocecal tuberculosis Regional ileitis or Crohn s disease is a chronic inflammatory process which most often involves the lower ileum A mass may be formed which may resemble an appendiceal abscess or abscess from some other cause The disease however usually affects young adults and the picture is a more chronic one It really may be said to resemble that of an appendicitis spread over months rather than days

The commonest lesion to occur in the right lower quadrant of course is appendicitis In the present case the abruptness of onset the vague initial symptoms the acute pain following the taking of a cathartic the persistent vomiting and the subsequent development of an inflammatory mass suggest that the patient had a ruptured appendix with localized peritonitis and abscess formation This could account for the subsequent development of the bowel symptoms and the progressive anemia which is not uncommon in chronic infections of this type Appendicitis may run an atypical course in older individuals In this patient additional diagnostic difficulties were imposed by extreme obesity A major possibility in an obese woman known to have diverticula is infection of a diverticulum with leakage and abscess formation This is somewhat unusual on the right side but gains some support from the x ray evidence of a mass displacing the sigmoid The displacement of the sigmoid may have been associated with myomatous changes in the uterus I am inclined to believe that this patient had appendicitis with rupture The peritonitis was probably localized It seems likely that there was also venous thrombosis of the portal system

Anatomical Diagnosis (Autopsy No 14547) Perforated gangrenous app ndix Multiple abdominal adhesions walling off localized areas of peritonitis Hemorrhagic colitis Extensive thrombosis of pelvic veins

Thrombosis of both iliac and femoral veins and pulmonary arteries Edema both legs Miliary abscesses right kidney Myomata uteri Arteriosclerosis aorta and coronary arteries Obesity Pulmonary edema Ulceration esophagus

There was an appendicitis which was evidently of long standing with rupture and abscess formation among the adhesions It seemed probable that this led to the extensive thrombosis in nearby vessels The adrenal on the left side was completely cut off from its blood supply and the cells were all disintegrated The kidneys although there was thrombosis of the left renal vein showed no necrosis In the right kidney there were accumulations of leukocytes

SUMMARY This 59 year old Negro woman developed nausea and vomiting followed by right sided abdominal pain and diarrhea four weeks before admission During the succeeding month she continued to vomit and pass tarry stools Examination revealed fever generalized arteriosclerosis a thick abdominal wall with generalized tenderness to palpation an enlarged uterus and tenderness on both sides of the pelvis with thickening of the broad ligaments She continued to vomit the edema of the legs increased and she died 34 days after admission There was a progressive anemia but no leukocytosis The abrupt onset the nature and location of the pain and the evidences of infection suggested that she had APPENDICITIS WITH RUPTURE AND LOCAL ABSCESS FORMATION This diagnosis was confirmed at autopsy

XI

(#10830 Admitted March 3 1927 Died March 14 1927)

THIS 70 year old Negro man complained of pain in the stomach In the fall of 1926 he noticed weakness and the development of pain originating near the middle of the sternum and radiating toward the umbilical region It was further described as a dull ache so severe at times as to make him short of breath He had no chills or gastrointestinal symptoms After 3 or 4 days discomfort was so severe that he quit work Coughing and deep breathing were painful Nocturia developed with a frequency of 4–5 times per night One week before admission he acquired an upper respiratory infection followed by swelling and running of the eyes He noted no edema but had lost weight during the current illness

PHYSICAL EXAMINATION on admission T 98 4 P 68 R 20 B P 150/80

The patient was an emaciated elderly Negro man who was drowsy and uncooperative He complained of severe pain in the right side when moved The skin showed extensive desquamation but no eruption The mucous membranes were pale There was moderate generalized lymph node en largement with discrete and firm nodes There was a definite kyphosis Both eyes were prominent and the lids could not be raised to the full extent The other ocular movements were normal The pupils reacted to light and accommodation There was a moderate mucopurulent discharge from both eyes The fundi were not visualized The trachea was displaced slightly to the right There was an increase in the anteroposterior diameter of the chest and kyphosis of the thoracic spine The right side of chest bulged more than the left and there was fullness of the intercostal spaces Anteriorly on the right the percussion note was dull below the clavicle The dullness increased at the level of the 2nd rib and the note became flat below the 3rd rib anteriorly and the angle of the scapula posteriorly Toward the spine there was a narrow strip where the percussion note was only slightly impaired The breath sounds were virtually absent over the area of flatness The voice sounds were suppressed There was no egophony No rales were heard except at the extreme lung base The heart was normal The pulses were equal and synchronous and the vessel walls were thick ened The abdomen showed increased fullness in the right hypochondrium The liver was palpable 4 fingerbreadths below the costal margin The edge was smooth and the surface seemed a little irregular The spleen and kidneys were not palpated An easily reducible inguinal hernia was present on the right The genitalia were normal and the rectal examination was

negative No edema or clubbing was noted The reflexes were present and equal

COURSE IN THE HOSPITAL The patient remained drowsy There was an irregular elevation in temperature of moderate degree A right thoracentesis was performed with removal of 600 ml of chocolate colored material of the consistency of thin paste Degenerated cells were seen on smear mostly lymphocytes with some polymorphonuclear cells A guaiac test on the fluid was strongly positive Cultures of this material showed a heavy growth of *Staphylococcus aureus* It was believed that the patient had an encapsulated empyema although the etiology was obscure He became incontinent of urine and feces On March 10 a cannula was fixed in place for irrigation of the empyema cavity There was considerable serosanguinous drainage from the cannula Later prior to death much thick bloody purulent material was removed

LABORATORY DATA Blood serologic test for syphilis was negative Red blood cells 4 4 million hemoglobin 50% color index 0 55 Leukocyte count 26 000 with 92% polymorphonuclear cells 6% lymphocytes and 2 monocytes Blood smear showed many pale red cells and slight anisoand poikilocytosis Urine showed a trace of albumin many white blood cells no red cells or casts Guaiac test and test for bile negative Nonprotein nitrogen was 41 mg % creatinine 1 6 mg %

Guinea pig inoculated with empyema fluid died 6 days later with staphylococcal abscess at the inoculation site Culture of material from eye showed a heavy growth of *Staphylococcus aureus*

Radiological examination of the chest showed encapsulated fluid in right chest On March 8 the right diaphragm was elevated There was a dense shadow along the right axillary border due to encapsulated fluid probably some air in area of encapsulation

DISCUSSION We may begin by focusing our discussion upon the presence of fluid in the chest Whenever one inserts a needle through the thoracic wall and withdraws pus it is highly probable that the patient has an empyema However other lesions may simulate empyema An abscess cavity in the underlying lung substance may be difficult to distinguish from empyema Fluid withdrawn from the lower portion of the chest on the right side may have originated in a subdiaphragmatic abscess or an abscess within the liver which has extended into the pleural cavity If the history the symptoms and the physical signs do not serve to differentiate between these various conditions by the time pus is evacuated the surgeon s finger may be inserted through the thoracotomy wound and palpation may determine whether the diaphragm is above or below the collection of pus This was not possible in the present case because the simplest drainage procedure was chosen in view of the critical condition of the patient

If this were an empyema then it was most likely postpneumonic or tuberculous or a complication of some underlying pulmonary infection The chocolate color of the pus its bloody character after introduction of the catheter and the anemia all suggest that there might have been considerable bleeding into this lesion This would suggest the possibility of a vascular lesion perhaps a syphilitic or dissecting aneurysm which had leaked into the pleural cavity the bloody material becoming infected Numerous possible types of pulmonary suppurative disease with abscess formation must be considered There may have been a simple abscess with a mixed infection There may have been an underlying specific infection such as tuberculosis actinomycosis or amebiasis One must also consider the possibility of an abscess secondary to bronchial obstruction due to bronchogenic carcinoma enlarged lymph nodes tuberculosis an aneurysm or aspiration of a foreign body or food There was no evidence of any penetrating wound of the chest wall Pulmonary suppuration may complicate other diseases such as pulmonary infarction congenital cystic disease of the lungs bronchiectasis or hydatid disease

The next possibility is that this disease originated below the diaphragm The pain in the chest began at the mid portion of the sternum and radiated down to the level of the umbilicus This might have been associated with an ulcer or neoplasm in the lower esophagus in the cardiac end of the stomach or along the lesser curvature Subdiaphragmatic abscesses due to these lesions are more likely to localize under the left leaf of the diaphragm It is also possible that this illness originated with either an amebic or a purulent infection of the liver which involved the subdiaphragmatic space and later extended into the pleural cavity

The anemia and the presence of considerable amounts of old blood in the evacuated material may be the key points in this case The findings are against a simple chronic encapsulated empyema either pneumococcal or tuberculous in origin The long course of events after the original pain would be unusual for an aneurysm Pulmonary suppuration with lung abscess formation and extension to the pleura is frequently associated with necrosis of pulmonary tissue and bleeding into the lesion Amebic infections also may be associated with hemorrhage into the lesions and the character of the pus in the present case chocolate in color and having the consistency of thin paste is typical of an amebic abscess If the empyema were due to bronchial obstruction with abscess formation behind a neoplastic lesion hemorrhage might well take place into the pus

Although pulmonary neoplasm with secondary suppuration is a more common cause of empyema in this locality, an amebic abscess is strongly suggested by the peculiar character of the pus Additional points of interest are the absence of fever sweats and chills and the lack of any history of raising sputum The absence of severe constitutional symptoms the lack of sputum production and the enlargement of the liver are all suggestive of an amebic infection originating below the diaphragm

ANATOMICAL DIAGNOSIS (Autopsy No 9750) Amebic dysentery with ulceration Abscesses of liver Encapsulated empyema lower part of right upper and top of right lower lobes

The right lung was covered by a fibrinous exudate extending from the base to the apex In the middle portion it was most profuse thick sharply circumscribed and virtually walled off Between two of the lobes there was a sealed off cavity with a hemorrhagic lining There were patches of pneumonia throughout the lung but no abscesses

Microscopically there was ulceration in the large intestine with accumulations of bacteria containing purulent material These ulcers were full of amebae and it was evident that the abscesses in the liver must be old amebic infections with secondary bacterial infection

The right lobe of the liver was almost completely replaced by two hug abscesses with a soft grayish yellow shaggy lining One cavity was surrounded by a wall of fibrous tissue 1 cm thick in places The larger of the two cavities presented under the capsule of the liver which formed its upper wall The diaphragm was adherent There was a ragged hole with about the same diameter as that of the trocar used for drainage The hole passed through the substance of the liver into the smaller of the two cavities and was probably the operative drainage site The liver substance about the abscess was compressed and a little icteric

The cecum contained numerous large elevated grayish areas which had the appearance of being composed of several layers of gauze Further down the large intestine there were many elevated yellowish firm areas which appeared to be the sites of lymphoid follicles but obviously had become necrotic There was one definitely healed ulceration

SUMMARY This 70 year old Negro man had had intermittent substernal pain radiating to the umbilicus for several months prior to admission Examination disclosed loss of weight pallor pulmonary findings indicating an accumulation of fluid in the right chest and hepatomegaly There was a marked leukocytosis and severe anemia Six hundred milliliters of chocolate colored material was withdrawn and trocar drainage instituted The fluid contained blood, and culture showed a heavy growth of staphylococci The possible causes of empyema of this type were discussed The peculiar character of the pus the enlarged liver the absence of sputum and of significant fever led to the diagnosis of amebic infection At autopsy there was AMEBIC DYSENTERY WITH INTESTINAL ULCERATION ABSCESSES OF THE LIVER AND ENCAPSULATED EMPYEMA

XII

(#397061 2d admission November 22 1946
Died January 11 1947)

THIS 58 year old white female entered because of a flaccid paraplegia Cervical adenopathy had been present for several years She lived on a farm Diabetes mellitus was diagnosed in 1926 but was controlled on diet alone

During the summer of 1945 she developed chills fever weakness fatigue malaise and night sweats The chills recurred every few days Her doctor made a diagnosis of undulant fever and said that agglutination tests were positive The symptoms abated during the winter of 1945–46 but recurred in milder form in the spring and summer of 1946 consisting mainly of evening fever with weakness and chilly sensations During the winter of 1945 she had one episode of epigastric pain which was severe and cramping in nature and radiated through to the back and under the right scapula It subsided within a few hours and did not recur until June 1946 After that time the pain was present almost constantly although it varied in severity It was never accompanied by any gastrointestinal symptoms It was not related to meals to exercise or to the ingestion of fried or fatty foods Pain was also present in the left lower chest anteriorly and laterally being of a dull character and localized deep in the thorax It was also felt on the right side of the abdomen and beneath the right scapula She was hospitalized August 23 1946 for investigation of the cause of this pain

SUMMARY OF FIRST ADMISSION *Physical Examination* T 100 6 P 88 R 24 B P 120/70

The patient was an obese woman whose skin was dry somewhat loose and inelastic There were several firm non tender lymph nodes in the anterior cervical and submaxillary areas The thyroid isthmus was palpable The breasts were normal No jaundice or cyanosis was noted Eye examination revealed no abnormalities She was edentulous The neck was supple Trachea was in the midline The lungs were clear The heart was normal The peripheral pulses were equal on the two sides The abdomen showed a thick panniculus The liver was palpable 8 cm below the costal margin and tender The spleen also was palpable and tender There were numerous tortuous varicose veins over the lower extremities Neurological examination was negative

Agglutination tests performed for detection of Brucella were positive in a dilution of 1/320 The gallbladder did not fill with dye and at operation on September 6 a large gallbladder with a stone in the cystic duct was

removed The liver was slightly enlarged and there were several retracted white areas on its surface Microscopic examination showed chronic cholecystitis No culture was made of the bile

Course after Operation After operation she continued to complain of pain and there were several episodes characterized by elevation in temperature aching in the upper thoracic spine and shoulders abdominal cramps and sweating She was receiving aspirin so that one could not be certain about the febrile course of her illness Urine cultures showed an anaerobic streptococcus No cause for her continued pain was found Several blood cultures proved to be sterile The opinion was that she had malignancy of the liver Just before discharge on October 3 a bromsulfalein test showed 20% retention at the end of 30 minutes She was slightly anemic at discharge (hemoglobin 10 4 gm) The icterus index was normal The leukocyte count was never above 7 500 and the differential count was normal Examination of stools showed no parasites and most specimens were negative for occult blood Examination of catheterized urine specimens showed no abnormalities

The pain in the back and lower thorax continued radiating bilaterally along the costal margins On October 22 her gait became ataxic and her legs weak They ached and were cold and rather cyanotic She had periods of mental confusion She re entered the hospital for diagnosis of the cause of her paraplegia

PHYSICAL EXAMINATION on second admission (November 22 1946 to January 11 1947) T 98 6 P 108 R 22 B P 110/70

The patient was apathetic with retarded activity due to hypnotics There was no adenopathy or cyanosis There was evidence of recent weight loss Moderate tenderness was noted over the 8th thoracic vertebra and over the 8th rib just lateral to the spine The pupils were normal The fundi showed no changes The tongue was red the tonsils enlarged The neck was not rigid The trachea was in the midline Expansion of the chest was limited but symmetrical The left diaphragm seemed to descend less well than the right There was dullness to percussion posteriorly to the left of the spine with diminution of breath sounds and bronchovesicular breathing No rales were present The liver was enlarged and the spleen was palpable The uterus was enlarged but no adnexal masses were made out Rectal examination was negative Neurological examination showed almost complete flaccid paralysis of the lower extremities There was bilateral ankle clonus The reflexes were very active Babinski reflexes were present on both sides There was thought to be some weakness of the upper extremities more marked on the right with a questionable Hoffman sign on the right Sensation was not impaired

COURSE IN THE HOSPITAL The patient complained bitterly of pain in the back For the first two weeks she ran little fever but from that time on there were elevations of temperature to 103 with marked tachycardia She developed urinary incontinence and tidal drainage of the bladder was instituted She developed extensive bed sores which became infected and also an *Escherichia coli* infection of the urinary tract Her condition rapidly deteriorated On January 2 a systolic murmur was noted at the

apex of the heart and fluid was present in the abdominal cavity Swelling of the submaxillary lymph nodes developed during the final stages of her illness She became unresponsive and died on January 11

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin 11 gm hematocrit 34 1 icterus index 3 leukocyte count ranged between 4 300 and 6 700 with normal differential count

Urine showed specific gravity 1 018 a few white blood cells and an occasional hyaline cast were present in the catheterized specimens Urine culture showed profuse growth of coliform organisms and *Streptococcus faecalis* Stool examination was negative for occult blood Blood nonprotein nitrogen was 27 mg % sugar 108 mg / CO_2 combining power 31 8 mEq chloride 101 6 mEq serum proteins 6 gm % cholesterol 207 mg / bilirubin total 2 5 mg / with 1 4 mg / direct alkaline phosphatase activity 8 7 Bodansky units Bromsulfalein retention was 46/ in 30 min thymol turbidity and cephalin flocculation test normal agglutinations for Brucella negative Blood cultures on two occasions were sterile

Lumbar puncture showed evidence of a block with no rise in pressure on jugular compression The fluid was xanthochromic with 600 mg % protein

X ray examinations on November 25 1946 showed minimal hypertrophic changes in the cervical spine The heart was at upper limits of normal in size The aorta was dilated and tortuous The lung fields were clear There was a rounded shadow projecting from the mediastinum on the right in the region of the root of the aorta On December 2 1946 x ray of the thoracic spine showed the body of the 7th thoracic vertebra was almost completely destroyed and revealed a mass subjacent to the destroyed vertebra

DISCUSSION The central feature of this illness was the spinal cord compression secondary to a lesion of the 7th thoracic vertebra In reviewing the course of this illness it seems reasonable to assume that the pain which was never accompanied by any gastrointestinal symptoms was probably not related to the gallbladder but was due to root irritation secondary to the vertebral lesion This is not common in spinal caries due to tuberculosis but it is the first symptom in a majority of other vertebral lesions and may be the only symptom for many months It assumes various forms a dull ache a neuralgic pain a feeling of constriction or so excruciating a pain as to demand large doses of hypnotics It may be constant or intermittent The skin at first may be hypersensitive in the painful area

Although variations are common in most cases the cord symptoms arise in the following order first weakness spasticity and ataxia then impairment of sensation the sensations of position passive movement temperature pain and touch being affected in progression Defective sphincter control often precedes and sometimes follows sensory loss Ultimately the limbs become flaccid and muscle

wasting occurs Increase in tone in the extensor group is characteristic of the interruption of the pyramidal tracts In cases in which the lesion is more extensive certain extrapyramidal pathways are injured and the extensor muscles lose their tone as was apparently the case in this patient

Examination of the spinal fluid in this case revealed the loculation syndrome which is characteristic of cord compression In its complete form it consists in a great increase in the amount of albumin and a yellow color in the fluid with no significant increase in cells These changes are found below the site of compression only The dynamics were incompletely recorded hence they cannot be adequately discussed

We may now consider the various lesions which might have produced *spinal cord compression* in this case

(1) New growths may occur in the membranes or in the substance of the cord itself so called extramedullary and intramedullary tumors I know of no situation in which these spinal cord tumors invade bone to the extent of causing collapse of a vertebra

(2) Tumors may arise from the vertebrae themselves Sarcoma is the commonest primary malignant tumor It may arise in the bone or periosteum of the bodies or laminae Growth is rapid and the cord is compressed by the growth itself or by displaced bone Secondary sarcoma is not so common but may arise as metastasis from sarcoma of bone elsewhere for which there was no clinical evidence in this case Nor have we any evidence to suggest that the bone was involved by a growth originating in adjoining soft parts such as those of the mediastinum

Carcinoma of the vertebrae does not occur as a primary tumor but is a frequent and distressing complication of cancer elsewhere The bodies laminae and intervertebral discs of several adjoining vertebrae may be so infiltrated as to cause complete destruction of extensive portions of the spinal column The diseased areas may collapse deformities are readily produced the cord is compressed and nerve roots are infiltrated by growth or pinched between fragments of bone As a result a most distressing clinical picture is produced A very small tumor in the breast thyroid lung or kidney may produce extensive disease of the vertebrae Primary tumor of the liver with vertebral metastasis which was the clinical diagnosis in this case at the time of death is extremely unusual On clinical examination no masses were felt in the breasts and no enlarged axillary nodes were described The thyroid was said to be normal and there were

no localizing signs in the chest The kidneys were not palpable and there was no hematuria Hodgkin s disease or lymphosarcoma must be considered as possibilities The liver involvement is compatible with either the spleen enlargement is compatible with Hodgkin s disease but this is less common in lymphosarcoma There was never any conspicuous lymph node enlargement and I believe that either of these possibilities is unlikely Other diseases must be mentioned such as myeloma and melanotic sarcoma but there is nothing in the way of positive evidence to support the existence of any of them Benign tumors of the spine such as osteoma and chondroma may encroach on the lumen of the bony canal but usually grow forward and in any event could not account for the other features of this illness

The x ray report in this history said that the vertebral changes were most likely due to vertebral metastases and this was the clinical impression of many who saw this patient However I believe that the clinical picture as a whole fits better with an infection A variety of acute and chronic inflammatory processes may involve the vertebrae Bacteria may lodge here during the course of bacteremia due to any of a number of organisms

Tuberculosis of the vertebrae or spinal caries affects the cord in about one case in 20 Compression arises most often from disease of the thoracic vertebrae as in this case There are many mechanisms by which the caries may lead to compression and although pachymeningitis is the most common it may be secondary to a paravertebral abscess which the x ray shows was present here Root symptoms are rarely present as the intervertebral foramina which lie close to the axis around which the bodies and spines rotate during displacement are not narrowed and the roots escape damage Paralysis due to caries unless it follows trauma does not usually develop as rapidly as in this case This is an uncommon age for tuberculosis of the vertebrae and there are other features of the illness which are difficult to explain on this basis

Syphilis may produce changes in the vertebrae with enough destruction of bone to result in collapse This is rare and usually occurs in the cervical area Aneurysm of the aorta also may cause vertebral erosion and cord compression This patient had a negative Wassermann test

An additional possibility is suggested by the positive Brucella agglutinations Spondylitis is not an uncommon complication of brucellosis and it may be accompanied by paravertebral abscess forma

tion Although I have never seen cord compression in this disease its occurrence might reasonably be expected Let us assume that the pain was not associated with gallbladder involvement How does this picture fit with a diagnosis of chronic brucellosis with spondylitis paravertebral abscess formation and spinal cord compression?

(1) The symptoms lasted with exacerbations and remissions over a period of 18 months

(2) Onset occurred in July 1945 with chills fever weakness malaise and night sweats Symptoms disappeared during the winter of 1945–46 but then there was a return of fever weakness and chilly sensations The pain during that winter was unlike gallbladder pain since it was always bilateral and was never accompanied by any gastrointestinal disturbances

(3) The patient entered the hospital in August 1946 because of pain Agglutination and complement fixation tests for brucellosis were positive Liver and spleen were enlarged She had intermittent bouts of fever The gallbladder was removed without relief of pain

(4) In October 1946 there was onset of weakness and ataxia of legs and marked nervousness

(5) In November 1946 the patient was found to have paraplegia with high spinal fluid protein with few cells With development of a loud murmur at the apex of the heart one might speculate as to the possibility of brucella endocarditis

Hepatitis is seen in brucellosis as is enlargement of the spleen Metastatic lesions in vertebrae are well known The absence of agglutinins in the blood during the latter stage of the illness is not disturbing There may have been a prozone phenomenon which obscured the agglutinins My final diagnosis is brucellosis because this seems to offer the best explanation of the course of the illness and the final clinical picture

ANATOMICAL DIAGNOSIS (Autopsy No 20360) Primary calcified tubercle lower lobe left lung and regional node Caseous tuberculosis of the 7th and 8th dorsal vertebrae with collapse of the 7th vertebra and compression of the spinal cord Paravertebral tuberculous mass right History of diabetes mellitus with extreme hyalinization of the islets of Langerhans Early cirrhosis of the liver Lobular pneumonia Infiltration of the splenic pulp with eosinophils Chronic cystitis Pyelonephritis left kidney Reticular zone adenoma of the left adrenal Endometrial and endocervical polyps Surgical absence of the gallbladder History of brucellosis

The spine was distorted and angulated A tumor mass with roughened overlying pleura protruded from the thoracic vertebrae on the right On section a white tumor mass was seen to infiltrate and distort the overlying

tissue This extended into the adjacent intervertebral disc which was partly softened and lost This tumor was soft and cheesy in appearance The area of vertebral distortion had compressed the vertebral canal and the cord was definitely distorted

Study of the microscopic sections showed tuberculosis of the vertebrae with almost complete destruction of the 7th dorsal The process extended into the 8th vertebra and there was a large caseous mass along the right side of this vertebra In the lung there was an old calcified primary lesion

SUMMARY This 58 year old white female developed brucellosis 18 months before death and later had severe episodes of pain in the epigastrium which radiated to the back and beneath the right scapula and was also felt in the left chest This pain was not accompanied by gastrointestinal symptoms or related to meals Examination three months before death revealed fever epigastric tenderness hepatomegaly and splenomegaly Brucella agglutination revealed a titer of 1/320 A dilated gallbladder containing stones was removed The pain continued and radiated along both costal margins Eight weeks before death the patient became ataxic and rapidly developed severe paraplegia There was evidence of loss of weight dullness over the left lower lung and a complete flaccid paraplegia There was destruction of the 7th thoracic vertebra with an adjoining mass The discussion centered about the various causes of vertebral involvement with spinal cord compression An inflammatory disease seemed more likely than tumor and although tuberculosis was considered a final diagnosis of chronic brucellosis with spondylitis was made Autopsy revealed caseous TUBERCULOSIS OF THE 7TH AND 8TH DORSAL VERTEBRAE WITH COLLAPSE OF THE 7TH AND COMPRESSION OF THE SPINAL CORD There was early cirrhosis of the liver

XIII

(#293784 Admitted September 30, 1946
Died September 30 1946)

THIS 43 year old Negro female had first been admitted on July 1 1943 with a mass in the left lower quadrant of the abdomen She had noted painful lumps in this area eight months before The pain became more severe and the mass grew in size There was no associated disturbance in menstruation urination or passage of feces In the beginning the pain was of a bearing down type but did not radiate At a later stage it spread to the whole lower abdomen and also into the lower back During the four months before entry there had been a 10 pound loss of weight

SUMMARY OF FIRST ADMISSION *Physical examination* showed that the patient was well nourished and did not look severely ill There was slight generalized lymph node enlargement The thyroid was not enlarged The breasts were normal The heart was not enlarged No murmurs were heard The lungs were clear The abdomen was protuberant In the left lower quadrant there was a tender mass about 15 × 17 cm attached to the anterior abdominal wall The kidneys liver and spleen were not enlarged There were a moderate sized cystocele and rectocele On pelvic examination the lower part of the abdominal mass was found to be close to the bladder The uterus was enlarged and in the posterior wall several myomas were felt On the left side in the adnexal region the firm movable and exquisitely tender mass could be felt extending up to the umbilicus Neurological examination was negative

An exploratory laparotomy was performed There was a stony hard mass involving about one third of the lower left anterior abdominal wall Its main portion was near the middle of the left rectus muscle No pelvic or skeletal structures could be felt connecting with this mass When the anterior rectus sheath was entered the tissue appeared to be quite indurated and had a fleshy color suggesting sarcoma The peritoneum was entered with difficulty at the upper border of the mass Omentum and loops of small intestine were adherent in the pelvis and infiltrated with what was thought to be sarcomatous tissue The patient had a swinging type of fever after operation She was placed on sulfathiazole because of a positive Frei test The temperature did not return entirely to normal She developed a sinus in the incision which continued to drain Her hemoglobin was 65 per cent at the time of discharge Sigmoidoscopic examination revealed no lesions of the sigmoid or rectum

Laboratory Data Blood serologic test for syphilis was negative

Urine was normal Hemoglobin was 10 7 gm leukocyte count 8 500 Frei test was positive tuberculin test negative An upper gastrointestinal series on July 28 was normal The barium passed slowly through the small intestine Barium collected in isolated segments in the ileum and the *mucosal pattern could not be demonstrated These changes suggested the* possibility of an inflammatory process Barium enema was normal Biopsy of specimen taken at operation rectus muscle tumor containing acute and subacute inflammatory tissue

SUMMARY OF SECOND ADMISSION The patient was readmitted on November 2 1943 A few weeks previously she had noticed a painful swelling to the right of the old incision There was pain over the mass and she had been feverish for several nights Examination revealed a soft fluctuant mass in the right lower quadrant surrounded by a bony hard area of induration 2–3 inches in diameter This was incised and drained with the release of a moderate quantity of thick viscid material Smears showed no acid fast bacilli Cultures showed no aerobic or anaerobic bacteria The hemoglobin was 10 gm leukocyte count 8 400 She had no fever

SUBSEQUENT COURSE After discharge the patient returned periodically for treatment of the draining sinuses They never healed completely On March 13 1944 she had diarrhea and pain on defecation She was steadily losing weight The abdominal mass was palpable and tender In October 1945 there was still drainage from one of the abdominal wounds She became incontinent of urine and was thought to have acute cystitis and pyelitis A specimen of urine obtained on cystoscopy was loaded with white blood cells and also contained 200–300 red blood cells per high power field Kidney function was normal Culture from the left kidney showed growth of *Escherichia coli* Left retrograde pyelogram showed no evidence of ureteral obstruction Calcified areas seen near the renal pelvis were thought to be in a lymph node Cystoscopy was repeated on December 21 1945 because of continued pain in both flanks A bladder specimen of urine contained 10 to 15 white blood cells per high power field occasional granular casts and an occasional red cell Right retrograde pyelogram showed dilatation of the renal pelvis and calyces Cultures showed growth of *E coli* and a paracolon bacillus When she returned on January 18 1946 after treatment with sulfonamides a bladder specimen was normal

She entered the hospital on September 30 1946 in a moribund state It was said that about five weeks before this admission she had developed a cough and pain in the side One week prior to admission there was some swelling of the ankles

PHYSICAL EXAMINATION on third admission T 92 P 78 R 32 B P 102/68

The patient was emaciated The mucous membranes were pale There were two draining sinuses below the umbilicus emitting a greenish thin foul smelling material A small hemorrhage was seen in the retina above the right optic disc In the inguinal areas there were firm freely movable lymph nodes There were dullness and suppression of breath sounds at the

right lung base Over the entire right lung and at the left lung base there were fine crackling rales The cervical veins were not engorged The border of the heart was 11 cm to the left in the 5th interspace 2 cm to the right in the 4th interspace The heart sounds were distant no murmurs were present The abdomen was distended The liver was slightly enlarged There was edema of the lower legs She died a few hours after admission

LABORATORY DATA Culture from the abdominal sinus showed an organism of the coli aerogenes group as did the culture from the blood Hemoglobin 3 gm hematocrit 22 icterus index 15 sedimentation rate 26 mm per hour Mean corpuscular volume was 112 mean corpuscular hemoglobin 31 mean corpuscular hemoglobin concentration 33 There was some macrocytosis no sickling was seen Leukocyte count was 3 800 with 10% juvenile neutrophils 57% segmented neutrophils 2% eosinophils 26% lymphocytes and 5% monocytes Catheterized urine specimen showed a trace of albumin sediment was normal Portable x ray of the chest showed dense irregular mottled clouding involving all of the lob s of each lung but most prominent in the right upper lobe There was a pleural reaction with some fluid in the right hemithorax and slight collapse of this lung

DISCUSSION We are dealing here with a chronic illness which progressed over a period of about 3 years It was characterized by masses in the lower abdomen involving the abdominal wall and lead ing to the development of chronic sinuses progressive emaciation and macrocytic anemia The cause of this illness was probably a chronic type of infection although neoplastic disease was not ruled out with certainty Among the possibilities which must be considered are tuberculosis lymphopathia venereum syphilis lymphoblastoma actinomycosis other granulomatous diseases involving the intestine such as chronic stenosing regional enteritis and an infection originat ing in a diverticulum

Sinus formation of a chronic type was an outstanding feature of this case and there are a variety of conditions which must be con sidered under these circumstances several granulomatous diseases may develop in the lower abdomen Peri intestinal granulomas sec ondary to sealed off perforations of the bowel may be due to fish bones or toothpicks or associated with a ruptured diverticulum Occasionally the lesions of lymphosarcoma may be limited to the lower intestinal tract Regional ileitis or colitis is a chronic disease in which there is thickening of the wall of the gut frequently accom panied by attacks of diarrhea Intra abdominal masses may be pal pable and fecal fistulas may develop None of these possibilities seems capable of explaining this patient s illness

Neoplastic disease is probably but not entirely ruled out by the

operative findings The final pulmonary lesions may have been meta static It seems unlikely that the patient would have survived for a period of three years if a malignant tumor had been responsible for the extensive lesions found at operation

Lymphogranuloma venereum is characterized by involvement of regional lymph nodes In untreated cases the nodes gradually become adherent and form a single fluctuant inflammatory mass which may break through the skin and lead to chronic draining sinuses with mul tiple foci of suppuration The pus is usually thick and grayish and the nflammatory mass resembles that seen in tuberculous adenitis The inguinal type is most common in males but in females the bubo may develop unnoticed inside the pelvic girdle in the perianal or deep pelvic nodes In females the rectum is almost always involved with stricture formation which apparently was not present here The routine Frei reaction tells us that the patient had had this disease This reaction persists for many years after healing has taken place hence it may not be indicative of active disease

Localized tuberculosis of the peritoneum starting from an infection of the colon or mesenteric lymph nodes may lead to the formation of adhesions abscesses and finally draining sinuses The diffuse pul monary disease present just before death might have been due to disseminated tuberculosis The tuberculin test was negative and no acid fast bacilli were found in the pus from the draining sinus

Finally one must consider a mycotic infection Actinomycosis is a disease in which sinus formation is the rule Twenty to 30 per cent of the infections are primary in the abdomen Fever of an irregular type may be present and there may be pain nausea and vomiting sweats and loss of weight The condition may not be recognized until tumor like masses of uneven contour develop The lesions spread to the abdominal wall and sinuses and fistulas form It may invade the thorax erode vertebrae involve the spinal cord or extend into the pelvis As a terminal feature there may be a generalized dissem ination of the process Actinomycosis seems to be the most likely diagnosis in this case It is probable that the process had invaded the kidneys by direct extension The final complication was an *Escher ichia coli* bacteremia

ANATOMICAL DIAGNOSIS (Autopsy No 20179) History of abscess of right rectus muscle Draining sinus lower midline of abdomen Dissem inated actinomycosis with multiple abscess formation in lungs liver kid neys spleen and ovary Lobular pneumonia Small areas of necrosis one lung Pulmonary edema Fibrinous pleurisy Hydrothorax Fibrous peri

toneal adhesions Calcified subserous pedunculated myoma of uterus Malnutrition Multiple diverticula of bladder

In the left lower lobe there were small gray abscesses with softened centers Surrounding these were larger zones of hemorrhage and brown pigmentation Similar abscesses were scattered through the upper lobe The tracheal nodes were enlarged and uniformly gray The right lung duplicated the left in appearance The liver contained clusters of large confluent abscesses yellow in color with a periphery of translucent connective tissue suggesting actinomycosis The spleen had a thickened smooth capsule through which protruded opaque yellow foci which were extensions from small abscesses The kidneys showed a few coarse depressions on the surface and there were minute flecks beneath the capsule suggesting small abscesses many of which were rimmed by a hemorrhagic zone Behind the uterus and actually hanging from the bladder wall was a large nodule of encapsulated yellow partly calcified material which suggested an old calcified abscess On section the remaining ovary was replaced by translucent connective tissue in which there was one round yellow lesion with a soft center and a cluster of similar lesions extended throughout the entire gland

Microscopic sections showed that the lesions were due to widespread actinomycotic infection The portal of entry could not be established

SUMMARY In December 1942 this 43 year old Negro female had developed a tender abdominal mass and began to lose weight An exploratory laparotomy in July 1943 disclosed a large hard inflammatory mass attached to the right rectus muscle A draining sinus developed postoperatively Three months later a fluctuant lower abdominal mass was incised with drainage of viscid material The abdominal mass remained palpable and the patient continued to have draining sinuses In October 1945 she developed an acute cystitis due to *Escherichia coli* On September 30 1946 she entered the hospital in a moribund condition Examination revealed emaciation pallor two sinuses draining foul material extensive pulmonary abnormalities palpable inguinal masses hepatomegaly and peripheral edema The evidence seemed to indicate that this chronic progressive illness was due primarily to an infection rather than to a neoplastic process Actinomycosis was selected as the most likely possibility At autopsy it was found that the patient had ACTINOMYCOSIS with terminal generalized dissemination

XIV

(#393062 Admitted July 25 1946 Died October 9 1946)

THIS 69 year old Negro man complained of shortness of breath He had had episodes of bronchitis during recent winters accompanied by exertional dyspnea but never asthma Three weeks before admission he began to have increasing shortness of breath and developed anorexia and increased sweating Two weeks before admission he had four teeth extracted and developed headache and pain in the abdomen His respiratory distress increased and he had several attacks of nocturnal dyspnea Because of these symptoms digitalis therapy was instituted He failed to show any response and was admitted to the hospital

PHYSICAL EXAMINATION on admission T 100 P 118 R 28 B P 120/60

The patient was an emaciated Negro acutely and chronically ill with orthopnea and prolonged and labored expiration He was drowsy and irritable Minimal sacral edema was present There was no pallor or enlargement of lymph nodes There was bilateral arcus senilis The pupils reacted normally The retinal vessels showed moderate arteriosclerosis The thyroid was not enlarged The trachea was in the midline The jugular bulbs filled with the patient in a semi-erect posture The thorax was symmetrical in shape and emphysematous There was dorsal kyphosis The percussion note was hyperresonant except for dullness in the left axilla The diaphragm descended poorly The breath sounds were normal anteriorly posteriorly they were distant and at the left base almost absent although fine rales were audible In the left anterior axillary line there were scattered wheezes The precordium was quiet To percussion the heart was enlarged both to the right and to the left but was not displaced No shocks or thrills were present The sounds were distant and mushy in character The rhythm was regular and the peripheral pulses quick There was arteriosclerosis of the peripheral vessels The abdomen was rounded and distended There was dullness in the flanks The liver edge was not distinctly felt but dullness extended several fingerbreadths below the costal margin The reflexes were symmetrically active

COURSE IN THE HOSPITAL The patient s condition grew progressively more critical He continued to run a low grade fever and was dyspneic and orthopneic He was given Lanatoside C but there was little improvement On August 4 a thoracentesis was performed with removal of 300 ml of bloody fluid Red blood cell count of the fluid was 9 000 white count 1600 A queer cardiac arrhythmia developed The heart remained enlarged

both to the right and to the left On several occasions blood tinged fluid was removed from both the right and the left side of the chest This relieved the dyspnea only temporarily The abnormal signs in the lungs became less marked but a pleural friction rub was noted on several occasions The pulse rate remained high fever continued and he lost weight progressively The lesions noted in the x ray picture of the chest increased and new areas of density appeared There was no significant change in the size of the liver He gradually lost strength and died

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin was 12 gm sedimentation rate 26 mm per hour leukocyte count 4 400 with normal differential Urine and stool were normal Blood nonprotein nitrogen was 37 mg % acid phosphatase 1 5 Bodansky units bilirubin 1 4 mg / total 0 9 mg % direct alkaline phosphatase 17 0 units bromsulfalein retention 2 4 mg % thymol turbidity 1 3 units chloride 95 3 mEq CO_2 combining power 27 6 mEq serum protein 6 13 gm % with albumin 3 25 gm % and globulin 2 88 gm % Blood cultures and cultures of the pleural fluid showed no growth Tuberculin test (second strength PPD) 3 plus reaction Agglutination tests for Salmonella Shigella tularemia Brucella and cold agglutinins were all negative Venous pressure was 110–120 mm H_2O

X ray examination of the chest on August 3 1946 showed marked increase in the transverse diameter of the heart in both directions The aorta was normal with some calcium in the arch Calcification was seen in each hilum as well as a non specific infiltration extending from lower pole of each hilum Increased density was noted in the left base probably fluid Upper lung fields were clear On August 19 x ray showed a small area of infiltration in the upper portion of the right lung field and several fluid levels at right base There was also an area of infiltration in lower portion of left lung Intravenous pyelograms on August 23 showed both kidneys concentrating dye no definite abnormality was seen X ray of the chest on August 29 showed the changes previously described had become more extensive A gastrointestinal series made the same day revealed no gross lesion in the stomach

Electrocardiogram on July 30 showed sinus tachycardia low voltage in limb leads and normal axis On August 3 it showed auricular fibrillation and low voltage in limb leads On August 7 it showed normal sinus rhythm and low voltage

DISCUSSION In this case one is confronted with a febrile illness in an elderly Negro man which was characterized at the onset by manifestations of heart failure and later by progressive loss of weight and spreading pulmonary lesions accompanied by hemorrhagic pleural effusions

Let us first consider the pulmonary disease A *bloody pleural effusion* is met with under a variety of circumstances

Neoplastic pleurisy whether primary or secondary frequently shows hemorrhagic fluid Primary tumors of the pleura are rare and

there was no evidence of such a lesion in this case A secondary neo plasm of the lung with involvement of the pleura and metastases in the liver and bones is more difficult to rule out The liver was large and had a reduced functional capacity Furthermore in the absence of jaundice of any significant degree the repeatedly high alkaline phosphatase activity suggested the possibility of involvement of bones One could not be certain that the progressive changes in the lungs did not represent metastases although as will be pointed out later another explanation seems more likely Diligent search was made to find a primary neoplasm but none could be located Rectal exam ination revealed a normal prostate and the acid phosphatase activity was normal Gastrointestinal x rays revealed no evidence of tumor The liver did not seem irregular in outline nor did it increase in size The pleural exudate was not examined for the presence of tumor cells In general the picture seems less like that of neoplastic disease than like that of a chronic infection or multiple infarctions of the lung

The pleural fluid which accumulates following pulmonary infarc tion may be hemorrhagic Infarcted areas in the lung may become infected with resulting production of localized abscesses or empy ema Such a complication is not usual unless the original embolus is infected There was no known source of infected emboli in this patient The blood cultures were sterile and no cardiac signs were discernible to indicate the possibility of valvular heart disease with bacterial endocarditis This patient had no circumscribed attacks sug gestive of pulmonary embolization and the character and type of progression of the infarcts in a patient with heart failure and impair ment of liver function should lead to more significant bilirubinemia A bloody effusion may result from tuberculosis of the pleura and it may be seen in the pleurisy secondary to advancing pulmonary tuber culosis There are several observations in this case which favor tuber culosis as the cause of the advancing pulmonary lesions The rapid increase in density of the lung lesions suggested an exudative process The course of the illness with fever and progressive loss of weight suggested a chronic infection There was never any leukocytosis and the tuberculin test was strongly positive I believe it most likely that this patient had disseminated tuberculosis and the multiple areas of pulmonary involvement were part of the process

This still leaves certain features of the patient s illness unexplained When he was first seen the degree of pulmonary involvement was not alone sufficient to explain the dyspnea The heart was enlarged

there was some engorgement of the veins the liver was enlarged, peripheral edema was present If we assume that there was functional impairment of the heart what type of cardiac disease was responsible? The blood pressure was always normal there was no evidence of congenital or valvular heart disease, and the picture was never suggestive of hypertension in the pulmonary circulation We are then left with two possibilities which must be discussed in greater detail—disease of the myocardium or disease of the pericardium

In the presence of probable pulmonary tuberculosis large calcified mediastinal lymph nodes and great enlargement of the heart to both the right and the left one must give first consideration to the possibility of tuberculosis of the pericardium This patient obviously did not have severe constrictive pericarditis as the venous pressure measurements in the hospital were only at the upper limits of normal Might this illness have begun with rupture of a tuberculous mediastinal node into the pericardium? An acute pericarditis might have developed without severe constriction of the heart as is the case in most patients with tuberculous pericarditis and death resulted from further dissemination of the tuberculosis This is frequently the cause of death in patients with clinically recognizable tuberculous pericarditis Thompson has called attention to the occurrence in old people of tuberculosis of the pericardium associated with signs of progressive heart failure In many of these patients there was evidence of recent miliary spread of the tuberculosis and the cardiac picture was usually ascribed to arteriosclerotic heart disease Many features of this case suggest pericarditis The heart was greatly enlarged to right and left the precordium was quiet and the heart sounds were distant the electrocardiogram always showed low voltage in the limb leads digitalis had little effect on the patient s symptoms Transient auricular fibrillation is frequently seen in pericarditis The absence of a pericardial friction rub is not too uncommon If the enlargement of the liver was due to pericarditis it is surprising that there was not a more definite elevation of the venous pressure

Most of the features of this case could also be accounted for by arteriosclerotic heart disease which is a far more common cause of cardiac failure in this age group In the absence of unequivocal signs of pericarditis and in the presence of known general arteriosclerosis arteriosclerotic heart disease must be placed high on the list of probable causes of cardiac failure However it is usually preferable to select one disease which will explain the entire picture Therefore I shall make a diagnosis of tuberculosis with involvement of the lungs and pericardium

ANATOMICAL DIAGNOSIS (Autopsy No 20200) Calcified nodules in both lungs and hilar nodes Old fibrocaseous subapical tuberculous lesion left Caseous tuberculosis left upper lobe with cavity formation Bilateral caseous pneumonia Obliterative pleural adhesions with multiple encapsulated tuberculous abscesses and hemorrhages Enlarged caseous mediastinal lymph nodes with extension to pericardium Organizing caseous tuberculous pericarditis Generalized miliary tuberculosis Central atrophy and necrosis of liver Aortic and intrarenal arteriosclerosis Focal myocardial scarring Atrophy of testes Cystic hyperplasia of prostate with chronic prostatitis Adenoma in kidney Encapsulated organizing hematoma in small intestine Esophageal diverticulum

The heart was encased in a coarsely thickened pericardium averaging 1 cm or more in thickness The center of the covering was partly caseous The pleura over both lungs was thickened and fibrous Numerous cavities surrounded by grayish consolidation of the pulmonary parenchyma occupied the upper portion of the left upper lobe and there was more of this type of consolidation in its lower third One of these cavities emptied into a widely patent bronchus the mucous membrane of which showed several small hard tubercles In the right upper lobe there was a small cavity with a fibrinous wall and a patchy pneumonic process about it There was consolidation in a small area of the upper tip of the right lower lobe A few lymph nodes were found which contained tubercles The liver showed many pearly tubercles scattered throughout its parenchyma

There were large caseous nodes attached to the pericardium and section showed that the tuberculous process had extended through the capsule of one node to the surrounding tissue It seemed altogether likely that the caseous and organizing tuberculous pericarditis had its origin from this node or from a similar one There were numerous disseminated tubercles some with caseous centers in the viscera

SUMMARY This 69 year old Negro laborer who had had chronic bronchitis with exertional dyspnea developed increased shortness of breath anorexia and sweating three weeks before admission Headache and abdominal soreness appeared and his respiratory distress progressed Examination disclosed slight fever tachycardia emphysema dyspnea orthopnea prolonged expiration dullness and rales in the left axilla increased precordial dullness distant heart sounds cervical venous distention and hepatomegaly He continued to have fever and did not improve with digitalization A persistent serosanguinous pleural effusion developed The heart remained enlarged to percussion and auricular fibrillation set in Pulmonary infiltration noted in x ray films increased in extent and density The tuberculin test was positive and there was leukopenia Analysis of the clinical picture suggested a chronic infection rather than carcinomatosis The progressive loss of weight the spreading pulmonary lesions the leukopenia and the positive cutaneous tuberculin test were considered to be strongly indicative of tuberculosis and it was believed that the cardiac findings could best be explained by tuberculous pericarditis Autopsy disclosed caseous TUBERCULOSIS OF LUNGS MEDIASTINAL LYMPH NODES AND PERICARDIUM AND GENERALIZED MILIARY TUBERCULOSIS

XV

(#383696 Admitted May 26 1946 Died May 27 1946)

THIS 47 year old Negro laborer was admitted with a diagnosis of acute cardiac insufficiency In 1944 a diagnosis of early syphilis was made He received ten injections of mapharsen He supposedly had chorea at the age of 10 years

In January 1946 he developed pneumonia and was treated with a sulfonamide The illness improved at first but on February 1 his neck became rigid He was admitted to a hospital and had on physical examination T 104 8 P 120 R 25 and B P 148/90 There was cervical rigidity No rash or petechiae were seen The fundi were normal The breath sounds were distant throughout and expiratory rhonchi were heard at both lung bases The heart was not enlarged and the sounds were normal in character A soft systolic murmur was heard just to the left of the sternum The hemoglobin was 8 6 gm Leukocyte count was 8 600 with a normal differential Spinal fluid contained 8 000 cells of which 80 per cent were polymorphonuclears A type XIV pneumococcus was grown Blood culture revealed the same organism on February 1 but cultures on February 3 4 and 6 and on April 6 were sterile Blood serologic test for syphilis was positive on February 5 and on March 19

He was given 30 000 units of penicillin every three hours and large doses of sulfadiazine The temperature had fallen to normal on the fourth hospital day Penicillin was discontinued on February 12 and on March 3 the temperature spiked to 102 4 No abnormalities were noted on examination at this time The blood culture was sterile but the leukocyte count was 30 000 Radiological examination revealed recurrence of the pneumonitis and penicillin therapy was resumed He did well and treatment was discontinued on March 14 On March 27 the left border of the heart was observed to be 1 5 cm outside the nipple line The systolic murmur described at this time was loudest in the aortic area and an aortic diastolic murmur was audible along the left sternal border The blood pressure was 160/80 and no peripheral signs of aortic insufficiency were noted Because of the possibility of syphilitic heart disease he was given 3 6 million units of penicillin during the next week

On April 30 he was transferred to the Johns Hopkins Hospital for further study On physical examination blood pressure was 140/70 No cyanosis or edema was present The pupils reacted normally The fundi were clear There was no venous distention The lungs were normal The heart was slightly enlarged to the left with a forceful impulse in the fifth interspace

10 cm from the midline The first and second sounds in the aortic area were almost absent and were replaced by blowing systolic and diastolic murmurs The latter was transmitted down the left sternal border There was a loud systolic bruit at the apex With the patient erect there was a loud snapping first sound in the mitral area preceded by a short presystolic murmur and followed by a systolic bruit The peripheral pulses were full but not collapsing A faint pistol shot sound was described The leukocyte count was normal there was no anemia and the urine was clear The venous pressure was 120 mm of saline and the circulation time 16 sec (arm to tongue) Electrocardiogram revealed normal sinus rhythm with upright T waves in all leads X ray examination of the heart showed some enlargement in the left ventricular salient Blood and spinal fluid serologic tests for syphilis were positive The patient had no fever and blood cultures were sterile

On May 26 he was admitted for the second time On May 22 he had developed substernal pain with some numbness in the left arm This sensation of numbness had been present for several weeks On May 24 he took a long walk and that evening his ankles were swollen The next evening he had an episode of paroxysmal dyspnea A similar attack the following night lasted several hours

Examination on admission showed the patient to be dyspneic and orthopneic The blood pressure was 190/110 The neck veins were distended and the venous pressure was 200 mm of saline The breath sounds were asthmatic in character throughout No rales were heard on inspiration The heart was enlarged with the point of maximal impulse in the anterior axillary line A gallop rhythm was noted but no murmurs could be heard because of the pulmonary wheezes There was pitting edema of the legs An electrocardiogram showed normal sinus rhythm sinus tachycardia and slight left axis deviation The S T segments were normal The patient died suddenly the day after admission

DISCUSSION The problems in this case are the cause of the aortic insufficiency and the reason for the rapid development of acute cardiac insufficiency and death There can be little doubt that there was aortic incompetence The type of murmur described might have had its origin in the aortic or pulmonic valve but there were definite peripheral evidences of aortic insufficiency with enlargement of the left ventricle and no suggestion of preponderant hypertrophy of the right ventricle or unusual prominence or increase in pulsation in the pulmonary vessels

Three possibilities present themselves as potential etiologic factors for this valvular involvement (1) rheumatic fever (2) syphilis (3) acute bacterial endocarditis developing on a normal valve a bicuspid valve or a valve previously damaged by rheumatic fever or syphilis

The patient had a vague history of chorea at the age of 10 years

no other evidence of rheumatic fever in the past There was also a history of syphilis, but there had been no history of any chest discomfort, dyspnea or other evidences of cardiac involvement prior to his admission with pneumococcal meningitis The crucial point in the diagnosis centers about the cardiac findings at that time The heart was normal in size and the only abnormality described was a systolic murmur which might have been due to the anemia and fever The cardiac findings were not recorded again for nearly eight weeks at which time the heart was enlarged and a loud diastolic murmur was audible

It seems quite unlikely that the patient should have developed a full blown aortic insufficiency due to syphilis while being treated with penicillin Rheumatic valvulitis is also unlikely if the findings on the initial examination were accurate

When one considers the possibility of an acute bacterial endocarditis due to the pneumococcus then the various events seem to constitute a clear and understandable sequence The patient was steadily improving from a pneumococcus pneumonia when he suddenly developed meningitis This is not infrequently attributable to pneumococcus endocarditis especially when there is no sinus, ear, or mastoid involvement to account for it The progression of the cardiac signs under observation is readily explained on this basis No petechiae were described but embolic phenomena are not as common in acute as in subacute bacterial endocarditis The meningitis might have been the result of a cerebral embolus

It is difficult to predict whether the endocarditis was engrafted on a normal a syphilitic or a congenitally deformed valve The aorta was described as normal in the x ray examination and none of the clinical manifestations of aortitis were described prior to the acute illness Under these circumstances it seems unlikely that there was enough syphilitic disease of the aorta to cause a mechanical strain It is impossible to determine on the basis of clinical evidence the presence of a bicuspid aortic valve

The cardiac insufficiency apparently developed quite rapidly just before the patient s final admission to the hospital The chief manifestation of failure was acute pulmonary edema typical of that seen secondary to left ventricular strain There was also evidence of coronary insufficiency which is not uncommon in severe aortic insufficiency The heart sounds were obscured by the respiratory sounds so that possible changes in the character of the murmurs could not be recorded It is one of the unfortunate paradoxes of the modern

therapy of bacterial endocarditis that while penicillin may cure the infection heart failure may result from the increased valvular defect caused by the healing of the vegetations This is particularly true of aortic valve lesions where sudden rupture of an eroded healed cusp may occur

ANATOMICAL DIAGNOSIS (Autopsy No 19970) History of pneumonia and meningitis due to type XIV pneumococcus 5 months before death with subsequent development of aortic insufficiency Perforation of cusp of aortic valve with organizing vegetation Cardiac hypertrophy and dilatation Chronic passive congestion of lungs liver and pancreas Anasarca Infarct in left lower lobe of lung Scarring and chronic inflammation in pleura and splenic capsule

The heart was enlarged the left ventricle hypertrophied and slightly dilated The right leaflet of the aortic valve contained an oval hole 7 mm in length Sections from the margin showed scarring and a small remnant of vegetation undergoing organization It seems altogether likely that this hole represented the perforation of a cusp that had been attacked by pneumococcal endocarditis There was generalized chronic passive congestion

SUMMARY This 47 year old Negro laborer had a history of treated syphilis He developed pneumonia which improved temporarily only to be followed by meningitis due to pneumococcus type XIV These organisms were cultured from both spinal fluid and blood There was a systolic cardiac murmur at the time of his first hospital admission and the hemoglobin was only 8 6 gm With intensive penicillin therapy his condition improved but during convalescence he developed fever and x ray evidence of pneumonitis Treatment with penicillin was re instituted Later an aortic diastolic murmur was heard and in view of a positive serologic test for syphilis he was given further treatment with penicillin Four months after the onset of the pneumonia he developed severe pulmonary edema and died shortly thereafter After considering the causes of aortic insufficiency it was concluded that the patient had healed bacterial endocarditis of the aortic valve At autopsy the aortic valve showed a vegetation undergoing organization and fenestration of a cusp The original lesion was undoubtedly an ACUTE ENDOCARDITIS DUE TO THE PNEUMOCOCCUS

XVI

(#374391 Admitted February 4 1946 Died February 8 1946)

This 26 year old Negro housewife complained of chills and sweats of three weeks duration She had had six pregnancies in seven years She had had fever chills and pain in the flank during a pregnancy 18 months previously

In October 1945 she had a spontaneous abortion which was followed by vaginal bleeding for 10 days She was treated with a sulfonamide Following this episode she noticed edema of the ankles Two weeks later she had a chill and pleuritic pain She was told she had bilateral pneumonia and was treated with sulfonamides After two weeks rest in bed she felt better but the symptoms returned two weeks after she resumed work At this time she was told again that she had bilateral pneumonia and was treated with penicillin for four days She remained in the hospital for three weeks This was six weeks before her admission to this hospital Three weeks before her entry at Johns Hopkins she had chills and sweats at night A few days later pain in the lumbar region developed There was frequency nocturia and some burning on urination She was given penicillin but the symptoms persisted and eight days before admission a diagnosis of acute pelvic inflammatory disease was made Following this she was given further treatment with penicillin at home but her symptoms persisted she developed dyspnea and pain in the left side of the chest began to cough up thin mucopurulent material and was brought to the hospital

Physical Examination on admission T 102 4 P 112 R 52 BP 110/70

The patient was a well nourished apprehensive Negro woman The respirations were rapid and shallow The scleras were icteric and there was pallor of the mucous membranes The eyes were normal The neck veins were not distended There were a few small axillary nodes The breasts were normal There was diminution of resonance at the left lung base with medium moist rales extending around to the left anterior axilla Rales of a similar character were heard in the right anterior axilla No friction rub was heard The heart was normal in size The rhythm was regular There was a low pitched systolic murmur heard over the entire precordium but best heard in the 5th interspace 4 cm to the left of the sternum The second aortic sound was louder than the second pulmonic sound There was a systolic thrill in the 4th left interspace near the sternum The liver and spleen were not palpable There was no edema

and no clubbing of the digits There was pain on manipulation of the cervix uteri and thickening and tenderness in both fornices

LABORATORY DATA Blood serologic test for syphilis was negative hemoglobin 8 5 gm sedimentation rate 23 mm per hour leukocyte count 14 800 with 4% juvenile neutrophils 76/ segmented neutrophils 1/ eosinophils 11/ lymphocytes and 8/ monocytes Urine had a specific gravity of 1 004 no sugar albumin 1 plus an occasional white blood cell a rare red blood cell and no casts bilirubin total 3 2 mg / with 1 8 mg / direct Sputum culture showed no pathogenic organisms Four blood cultures were taken all being sterile Sputum examination showed no acid fast bacilli Electrocardiogram showed no abnormalities X ray examination of the chest showed clouding of the left base changes most likely due to an acute pneumonic process There was some increased density at the right base A lateral view of the chest revealed clouding of the left lower lobe but no evidence of encapsulated fluid

COURSE IN THE HOSPITAL The patient ran an irregular fever while in the hospital On the first night her temperature rose She was placed on 80 000 units of penicillin every 3 hours The physical signs remained essentially the same Signs of consolidation persisted at the left base with a few scattered rales audible also at the right base On the morning of the fourth hospital day the patient appeared to be the same as before She was found dead a few moments later by the intern

DISCUSSION It is not difficult to construct a plausible explana tion of this patient s illness A previously well Negro woman has an abortion which is followed after an interval of about two weeks by fever chills and pleuritic pain Following this there are recurrent illnesses diagnosed as pneumonia There are good reasons for ques tioning this diagnosis It is known that soon after delivery the uterine sinuses are plugged with thrombi These may become infected and then extend to the iliac and femoral veins Thrombophlebitis of this type may persist for weeks and may give rise to repeated pulmonary emboli These in turn may lead to infarction abscess formation pneumonitis and occasionally pyopneumothorax

It seems reasonable to conclude that the bilateral recurrent pul monary lesions which this patient had were due to emboli and not to one of the primary forms of pneumonitis No pathogenic organ isms were found in the sputum the clinical course was not typical of primary pneumonia there was no dramatic response to antibiot ics Recurrent attacks of pneumonia of such frequency in a previously healthy individual are extremely uncommon Moreover a diagnosis of pneumonia would not afford a satisfactory explanation for her sudden death while under treatment

Before we accept pelvic thrombophlebitis with emboli to the lungs as the sole explanation for this patient s illness several unusual fea

tures must be considered with greater care Five months would be an unusually long time for this type of illness One would also expect the phlebitis to spread and nvolve the femoral veins Furthermore one observer in addition to hearing a systolic cardiac murmur noted a thrill just to the left of the sternum in the 4th and 5th interspaces No diastolic murmur was heard

So in view of the unusual length of this illness and the presence of a significant cardiac murmur and probable thrill, we have to consider whether we are dealing with an acute vegetative endocarditis This disease often originates from a serious local infection in some other part of the body such as pneumonia osteomyelitis gonorrhea or what may be postulated in this patient puerperal infection

As soon as we explore this possibility the absence of certain important criteria becomes evident There were no petechiae no clubbing of the fingers no detectable enlargement of the spleen and most significant of all blood cultures were negative on four occasions One must remember however, that acute vegetative endocarditis presents a different picture from that seen in the subacute variety The valves of the right side of the heart are affected much oftener than in subacute endocarditis The clinical picture of right sided endocarditis is one of repeated pulmonary episodes as in this case and systemic embolization is unusual Large numbers of bacteria are filtered out in the pulmonary bed and cultures of blood from the systemic circulation may show no growth Since the patient had received almost continual therapy with sulfonamides and penicillin this provides an additional explanation for the sterile blood cultures Profound anemia is uncommon in acute endocarditis clubbing of the fingers rarely occurs and the spleen being softer is not so easily felt as in the subacute form

In summary the repeated pulmonary episodes with development of jaundice the absence of pathogenic organisms from the sputum and the failure of response to antibiotics lead to the conclusion that this patient had multiple pulmonary infarcts Since there was abundant evidence of systemic infection two likely sources of emboli exist

(1) Pelvic thrombophlebitis
(2) Acute bacterial endocarditis of the right side of the heart originating from the puerperal sepsis

Of these two possibilities the latter seems more probable because of the duration of the illness and the presence of a cardiac murmur and thrill

Three questions remain to be answered

(1) On which heart valve was the infection lodged? The location of the murmur is probably deceptive It was not heard over the areas of the tricuspid or pulmonic valves to which we have limited our selves on other grounds From the descriptions the murmur was a little nearer the tricuspid area In the cases from this hospital which Thayer analyzed the tricuspid valve was far more commonly in volved than the pulmonic

(2) What organism attacked the valve? The four most common organisms in acute bacterial endocarditis are the pneumococcus staphylococcus gonococcus and hemolytic streptococcus Consider ing the source of the infection in this case one can probably narrow the choice to the streptococcus and the gonococcus Anaerobic streptococcus infections are more common in puerperal sepsis and the organisms may be difficult to grow from the blood stream so this organism is more likely to be implicated in the present instance On the other hand gonococcal infections in Thayer s series involved the right heart chambers in almost two thirds of the cases

Finally (3) what was the cause of the sudden death? Rupture of a mycotic aneurysm and fatal pulmonary embolism seem the most likely possibilities In view of the previous episodes pulmonary em bolism is more probable

ANATOMICAL DIAGNOSIS (Autopsy No 19794) Subacute bacterial endocarditis with huge vegetation tricuspid valve (gram positive cocci alpha *Streptococcus faecalis*) Septic emboli to lungs with early abscess formation and pneumonia Pulmonary infarcts Peculiar tubercle like lesions with giant cells in lungs liver spleen and lymph nodes (?Sarcoid) Chronic passive congestion of liver Jaundice Splenomegaly acute splenic tumor Chronic cystitis Chronic cervicitis

The right auricle and ventricle were enlarged Clinging to one cusp of the tricuspid valve there was a huge pedunculated vegetation large enough to block the tricuspid orifice The remainder of the valve was normal The right lung was covered with adhesions and there was an infarct in the lower lobe and also one in the upper lobe There were two infarcts in the upper lobe of the left lung and one in the lower lobe over which there was an organizing exudate Microscopic examination showed the vegeta tion on the valve to be clearly of bacterial origin Scattered about in the lymph nodes the spleen and the liver were peculiar aggregations of mononuclear cells and occasional giant cells No tubercle bacilli could be stained in these lesions They appeared to be sarcoid in nature having little to do with the final illness No evidence was found of chronic pelvic infection or thrombosis of pelvic vessels

SUMMARY This 26-year-old Negro housewife had a spontaneous abortion followed by edema of the ankles Two weeks later she had a chill

and pleuritic pain a diagnosis of pneumonia was made and treatment with sulfonamide given One week later a similar illness developed and *penicillin was administered Three weeks later she developed night sweats* chills pain in the lumbar region urinary frequency and nocturia Despite further treatment with pencillin the symptoms persisted and she developed cough dyspnea and pain in the left chest Examination on admission re vealed fever tachycardia tachypnea icterus pallor signs of consolidation of the left lower lobe and in the right axilla a systolic murmur and thrill in the 4th left interspace and tenderness and thickening in both fornices *on pelvic examination Laboratory studies disclosed anemia* leukocytosis slight albuminuria hematuria and elevated serum bilirubin The fever and pulmonary signs persisted despite penicillin therapy and she died suddenly on the 5th day It was concluded that the recurrent pulmonary episodes following the abortion might be due to pelvic thrombophlebitis with periodic release of emboli An alternate diagnosis *suggested by the* duration of the illness the systolic murmur and thrill and the anemia was ACUTE BACTERIAL ENDOCARDITIS Because of the repeated pulmonary episodes without evidence of emboli in the systemic circulation it was thought that the vegetations would probably be found in the RIGHT SIDE OF THE HEART At autopsy a huge vegetation due to the *Streptococcus faecalis* was found on a normal tricuspid valve There were numerous *septic infarcts in the lungs*

XVII

(#226848 Admitted November 12 1945
Died November 27 1945)

THIS 39 year old Negro female was admitted to the Gynecological Service with lower abdominal pain and vomiting She had had nocturia for several years Her blood pressure was 180/100 in 1941 and she was very obese

Two weeks before entry she developed headache localized to the occipital region A few days later she developed pain in the left lower quadrant which was intermittent She began to vomit and until admission retained no solid food There was no change in the character or color of her stools

PHYSICAL EXAMINATION on admission T 98 6 P 136 R 28

The patient was obese was breathing rapidly and looked acutely ill The skin and mucous membranes showed no lesions The pupils reacted to light and accommodation The thyroid was normal The lungs were clear The heart was enlarged to the left There was a soft systolic murmur over the entire precordium The sounds were normal the rhythm regular the blood pressure 180/95 The liver was felt 2 fingerbreadths below the costal margin The spleen was not palpable There was tenderness to palpation over both lower quadrants but no rigidity or spasm The cervix was lacerated and soft The fundus of the uterus was enlarged and irregular Adnexal pressure was very painful The deep tendon reflexes in the lower extremities were absent

COURSE IN THE HOSPITAL During the first two weeks there were occasional rises in temperature up to 100 2 to 100 6 The pulse rate ranged from 110 to 150 The patient was restless and apprehensive and at times her behavior was erratic She perspired profusely with the covers off although it was not excessively hot She continued to have nausea and vomiting occasionally vomiting small amounts of blood The respiratory rate remained rapid although repeated examination of the lungs revealed no abnormality It was thought that the tachypnea and tachycardia were secondary to disease below the diaphragm Examination under anesthesia revealed no findings in the pelvis other than those described There were no localizing neurological signs and no evidence of meningeal irritation The blood pressure fluctuated at times rising as high as 235/100 and at others being as low as 160/70 There was always a wide pulse pressure An exploratory laparotomy was performed on November 26 Just prior to operation the temperature reached 104 At that time her blood pressure dropped to 110/60 At operation the uterus was found to be enlarged with two intramural myomas The tubes ovaries and appendix were normal

There was no evidence of recent inflammation The kidneys felt normal There was no palpable adrenal tumor The stomach felt smooth The gall bladder was small and contained two stones After operation her pulse rate was around 200 and the rectal temperature rose to 105 and finally to 107 4 The patient rapidly became stuporous and comatose and died the following day

LABORATORY DATA A catheterized urine specimen was normal Hemoglobin was 10 5 gm hematocrit 34 5 sedimentation rate (corrected) 43 mm per hour leukocyte count 11 900 with 5% juvenile neutrophils 53% segmented neutrophils 34% lymphocytes and 8% monocytes Blood nonprotein nitrogen was 33 mg % chloride 99 mEq bilirubin total 1 3 mg % direct reacting 0 8 mg % total serum proteins 6 80 gm % with 2 81 gm % globulin Spinal fluid protein 20 mg % cell count 2 Wassermann reaction was negative Urine culture was sterile Sputum showed normal throat flora

Electrocardiogram on November 15 showed normal sinus rhythm rate 100 left axis deviation T waves were inverted in leads 1 2 and 4 Impression Left axis deviation and digitalis effect A subsequent electrocardiogram showed the same findings

X ray examination of the chest on November 13 showed an increase in the transverse diameter of the heart to the left Lungs were clear There was elevation of the right diaphragm

DISCUSSION This 39 year old Negro woman died of a fulminating illness of about four weeks duration death coming with hyperpyrexia shortly after an exploratory laparotomy She weighed almost 300 pounds which made physical examination difficult

In searching the record for some orienting feature of this woman s illness two things stand out as consistently present but without obvious explanation—tachycardia and tachypnea in the presence of normal temperature If one assumes that she did not have a generalized pyogenic bacterial infection and this seems reasonable in view of the low grade fever and white cell count one must consider the following possibilities

(1) Tuberculosis miliary
(2) Acute pulmonary fibrosis
(3) Cerebral tumor with invasion of or pressure on the hypothalamus,
(4) Chromaffin tumor
(5) Paroxysmal tachycardia
(6) Fulminating Graves disease ending with so called thyroid storm

There is little to support the possibility of *tuberculosis* None was demonstrated in the abdominal organs at operation or in the lungs by x ray, and it would be most unusual in miliary tuberculosis to

have during the acute phase of the illness a relatively normal tem perature except for a terminal hyperpyrexia

Acute pulmonary fibrosis seems ruled out by the absence of any real dyspnea or cyanosis and the absence of physical or x ray evi dence of disease of the lungs It seems possible that a *cerebral tumor with hypothalamic involvement* might have produced this picture Cardiovascular and respiratory regulatory centers as well as the cen tral thermostatic mechanisms are situated in this area However one would not expect a cerebral tumor to lead to death so quickly with out producing overt neurologic signs or some evidence of increased intracranial pressure

Chromaffin tumors may lead to attacks accompanied by tachycardia and hypertension Clinically these tumors may produce a picture simulating hyperthyroidism and the hypermetabolism present has led to thyroidectomy before the true nature of the illness was appre ciated An extra abdominal pheochromocytoma would be most un usual and we must accept the exploration of the adrenals as being negative Besides there were no well defined attacks no apparent correlations of elevated pulse rate and hypertension no disturbance in carbohydrate metabolism and the pupils were always recorded as normal

This patient could not have had an ordinary *paroxysmal tachycar dia* The fluctuations in heart rate were great and the tachycardia did not come and go precipitously Electrocardiograms never showed paroxysmal auricular or ventricular tachycardia Irregular rhythm was described on occasions and may have represented paroxysms of auricular fibrillation This leads to the last possibility on the diag nostic list

Many of the features in this case suggest the possibility of *ful minating thyrotoxicosis* She was restless and apprehensive There was evidence of heat intolerance and profuse perspiration Tachycardia and tachypnea were prominent Nausea and vomiting with watery bowel movements are not infrequently seen in thyroid crises and her death coming postoperatively with extreme tachycardia and hyper pyrexia fits the picture There are objections however to this diag nosis No eye signs were described These may be absent in ful minating Graves disease The thyroid was described as normal but this may have been deceptive as examination was admittedly difficult because of the extreme obesity The vomiting of blood and the major complaint of abdominal pain are difficult to account for There seemed to be some variability in the abdominal pain and tenderness

and she was in the premenstrual period when she entered the hospital The patient did vomit small amounts of blood but no gross blood was seen in the stools and she developed no progressive anemia or circulatory collapse I cannot make this case fit any single diagnosis but will say that she had

Myomata uteri
Hypertensive cardiovascular disease
Hyperthyroidism diffuse
Possible gastrointestinal ulceration with bleeding cause unknown as explanation of the pain and bloody vomitus

ANATOMICAL DIAGNOSIS (Autopsy No 19696) Hypertrophy and hyperplasia of thyroid epithelium Hyperplasia of thymus History of hypertension Hypertrophy of heart Recent laparotomy Slight fibrino purulent peritonitis Myoma of uterus Infarction in myoma Hyperplasia of bone marrow Pulmonary edema Sickle cell spleen ? Adenoma of liver Obliterated appendix Atrophy of ovaries Marked obesity

The heart was moderately enlarged and the right ventricle markedly dilated The fundus of the uterus was replaced by several large intramural myomas The thyroid on gross examination was large but no nodules were found on section In the microscopic sections of the thyroid there were widespread but patchy hypertrophy and hyperplasia with papillary formation of the acini There was also some lymphoid hyperplasia Some acini contained colloid others did not The epithelium of the acini rang d from cuboid to low columnar

SUMMARY This 39 year old Negro female with a previous record of hypertension developed occipital headache lower abdominal pain and persistent vomiting 2 weeks before admission Examination revealed obesity tachycardia slight cardiomegaly a systolic murmur and uterine enlargement with adnexal tenderness She had occasional elevations in temperature persistent tachycardia nausea and vomiting and excessive perspiration and intermittently behaved erratically The tachypnea and tachycardia were thought to be due to subdiaphragmatic disease The blood pressure fluctuated from 160/70 to 235/100 with a wide pulse pressure Exploratory laparotomy revealed only uterine myomas Prior to operation her temperature rose to 104 Postoperatively her temperature reached 107° the cardiac rhythm was irregular with a rate of 200 she became stuporous and died In view of the operative results the normal chest x ray and the normal neurologic examination the outstanding clues seemed to be tachypnea tachycardia wide pulse pressure with fluctuating systolic pressure and abnormal sweating even when the environmental temperature was normal The final diagnosis was HYPERTHYROIDISM with death in a thyroid crisis At autopsy the thyroid was found to be large and microscopically there were widespread patchy hypertrophy and hyperplasia of the acini

XVIII

(#56715 Admitted July 16 1934 Died September 21 1934)

THIS 37 year old white mechanic came to the hospital on April 11 1934 complaining of rheumatism In 1919 he had an attack of arthritis involving many joints This illness was of short duration and was followed by three years of excellent health Then he began to have brief attacks of arthritis which were never severe enough to keep him in bed Two months before his appearance at the hospital he sustained a Colles fracture of the right wrist Following this he had a severe attack of arthritis involving the shoulder hip knee and ankle on the left side In addition he complained of flatulence after eating and a feeling that his abdomen was swollen These symptoms present intermittently for two or three years were made worse by over-eating and by the ingestion of fried foods At the same time he began to have diarrhea with four to six watery bowel movements a day *Two years before admission he had an attack of painless jaundice which* lasted for about one week After this his abdominal distress was exaggerated He had a good appetite but ate little because ingestion of food aggravated his symptoms

At the time of his first visit he was found to be thin There was generalized pigmentation more marked in the folds of the skin The eyes were normal The teeth were in poor condition The cervical axillary and inguinal nodes were enlarged The thyroid was not enlarged The lungs were clear The heart was normal The abdomen was prominent It was soft and doughy The liver and spleen were not enlarged There was no ascites The remainder of the examination was negative except for stiffness and limitation of motion of all of the joints of the fingers moderate swelling of both knees and limitation of movement of both ankles

The condition of the joints improved but the patient continued to lose weight and the gastrointestinal symptoms grew progressively worse There was constant epigastric distress made worse by taking food The stools though not frequent in number had been watery and light in color

PHYSICAL EXAMINATION on admission T 100 4 P 90 R 20 B P 100/60

The patient was emaciated The deep tanning of the skin was noteworthy Numerous small lymph nodes were palpable in the cervical axillary and inguinal regions The fingers of the right hand showed fusiform swelling with ulnar deviation Both ankles were swollen and tender The lungs were clear except for dullness and diminution in intensity of breath sounds at the left base with a few moist rales at the bases of both

lungs The heart was normal The abdomen was distended and tympanitic There was no ascites no abdominal tenderness and no definite masses The edge of the liver was felt 2 cm below the costal margin The spleen was not enlarged There was diffuse resistance over the abdomen and on deep palpation indefinite masses could be felt Rectal examination was normal

Course in the Hospital The patient s temperature varied between 99 and 101 by rectum The pulse rate varied from 70 to 120 He had a constant diarrhea with blood in the stools as indicated by strongly positive guaiac tests His anemia progressed rapidly Proctoscopic examination was normal at the time of admission On September 20 he passed a large amount of dark red blood in his stool Preparations were made for trans fusions but death occurred quite suddenly from a large gastrointestinal hemorrhage

Laboratory Data On July 16 hemoglobin was 70% leukocyte count was 12 000 with normal differential On September 18 hemoglobin was 51°⁄ On September 21 hemoglobin was 30⁄ and leukocyte count 7 800

Urine examination showed a specific gravity of 1 027 no albumin or sugar occasional red and white blood cells no casts Stools were liquid to semi solid they presented a grayish color and had the consistency of creamy pus Microscopically only a few red and white blood cells were seen Repeated search failed to demonstrate any parasites Guaiac tests were strongly positive Stool cultures were negative for typhoid dysentery group of organisms There was no excessive amount of material which stained with Sudan III Fasting blood sugar was 75 mg % van den Bergh was normal Gastric analysis fasting showed presence of free hydro chloric acid total acidity 20° benzidine test was positive After histamine free hydrochloric acid was 100 total acidity 113

Glucose tolerance tests showed blood glucose 1/2 hr after 60 gm of glucose by mouth 96 mg % 1 hr 105 2 hr 110 3 hr 100 Sucrose tolerance test fasting 75 mg % 1 hr after 60 gm sucrose 86 mg % 2 hr 102 mg % 3 hr 95 mg % Bromsulfalein test of liver function was normal Intracutaneous tuberculin tests were negative

X ray of the chest showed lungs clear no evidence of metastasis Barium enema on July 19 the enema flowed without obstruction the sigmoid was rather narrow but did not suggest any lesion organic in nature the cecum was perfectly smooth Gastrointestinal fluoroscopy on July 20 showed normal stomach and duodenum The entire large intestine was spasti There was no evidence of any ulcerative lesion

Discussion The first important step in such a complex case as this one is to list the important symptoms the well documented physical signs the course of the illness and the important laboratory studies These seem to be

(1) Recurrent attacks of arthritis for 15 years which led to some joint deformity

(2) Digestive disturbances for three years characterized by diarrhea an intolerance to fatty foods and a feeling of distention

(3) A low grade fever and evidence of marked loss of weight

(4) Pigmentation of the skin but not of the mucous membranes

(5) Slight general lymphadenopathy

(6) Diarrhea with chronic blood loss and stools which had the appearance of creamy pus

The best focal point around which to orient the discussion would appear to be the chronic diarrhea The chronic nature of the complaint and the failure to find any pathogenic bacteria or parasites I believe adequately rule out the various forms of dysentery Arthritis may appear in chronic dysentery but the sequence of events is altogether against that possibility The character of the stools and the severe blood loss rule out any extra alimentary inflammatory disease as the cause of this patient s illness

The various types of steatorrhea (see Table 26) must be considered in view of the color of the stools and the flat glucose tolerance curve However these patients usually have a macrocytic type of anemia without as pronounced bleeding as this patient had Furthermore the stools were never described as bulky or foul smelling stains did not show unusual amounts of neutral fat and no abnormalities of the mouth or tongue were ever noted There was no evidence suggestive of chronic pancreatic disease and with a normal chest film and negative tuberculin test tuberculosis of the intestines or mesenteric lymph nodes seems unlikely Ulcerative colitis must be considered but the proctoscopic examination and the barium enema studies showed no characteristic lesions Regional ileitis is more difficult to rule out as adequate x rays of the small intestine were not taken However the course of the illness is against this and it would not afford an adequate explanation for the joint involvement Diverticulitis and neoplasm of the large bowel seem adequately eliminated by the radiological studies Thus it would seem that none of the ordinary *causes of chronic diarrhea* provide a satisfactory explanation for this complex illness and one is forced to seek a clue through some other channel This case presented manifestations in widely divergent areas—the intestinal tract and the joints There are a number of diseases which do involve many areas of the body and may simulate a wide variety of other diseases depending on the specific region of the body which is attacked Some of these are common diseases others are rare but it is helpful to keep a list of them in mind so that they may be systematically reviewed whenever

the pieces of a diagnostic puzzle do not readily fit together This is a situation in which it would be profitable to recall that list and see if it contains any good clues (cf Table 22)

(1) Tumors and granulomatous diseases
  (a) Sarcoidosis
  (b) Hand Schuller Christian disease
  (c) Leukemia
  (d) Multiple myeloma
  (f) Lymphomas
(2) Infections such as
  (a) Tuberculosis
  (b) Subacute bacterial endocarditis
(3) Metabolic diseases
  (a) Hemochromatosis
  (b) Hyperthyroidism
  (c) Primary amyloidosis
  (d) Intestinal lipodystrophy (Whipple s disease)
  (e) Addison s disease
(4) Collagen vascular diseases
  (a) Periarteritis nodosa
  (b) Systemic lupus erythematosus

As one looks over this list one notes several diseases which may produce chronic diarrhea From this point of view sarcoidosis lymphosarcoma Addison s disease intestinal lipodystrophy and systemic lupus erythematosus must, I think, receive more detailed consideration

Sarcoidosis may involve almost any area The duration of the patient s illness is consistent with this diagnosis as are the fever and lymph node enlargement I have however never heard of sarcoidosis producing a picture of chronic diarrhea in the absence of more characteristic manifestations of this disease such as splenomegaly or pulmonary lesions A lymphoma of such long duration with primary intestinal involvement would also be unusual Neither of these would provide a satisfactory explanation for the arthritis but we might be dealing with a newly acquired disease of the intestinal tract in a patient with chronic arthritis

Addison s disease was considered during life because of the cutaneous pigmentation and the tendency to low blood pressure However, there was no pigmentation of the mucous membranes and I cannot imagine a patient with this disease in an ill and debilitated state who would be able to secrete 100 degrees of free hydrochloric

acid into the stomach Furthermore one would not expect such severe bleeding to accompany the diarrhea of Addison s disease

Intestinal lipodystrophy is an interesting possibility This syndrome which was described by Dr George Whipple is characterized by gradual loss of weight and strength stools consisting chiefly of neutral fat and fatty acids indefinite abdominal signs and a peculiar

Table 26 Conditions in Which Steatorrhea May Develop
(Modified from table published in American Journal of Medicine vol 15 p 793 December 1953)

I Lack of enzymatic and other materials necessary for preparation of fats for absorption
  A Obstructive jaundice
    1 Hepatocellular
    2 Common duct obstruction
  B Pancreatic disease
    1 Chronic pancreatitis
    2 Cystic fibrosis of the pancreas
II Insufficient absorptive surface
  A After extensive resection of small intestine or stomach
  B Intestinal fistulas
  C Inadvertent gastroileostomy
III Defective absorption
  A Diseases involving intestinal tract or lymphatics
    1 Scleroderma
    2 Regional enteritis
    3 Lymphosarcoma
    4 Amyloid disease
    5 Tuberculosis
    6 Intestinal lipodystrophy
  B Sprue
  C Celiac disease
  D Chronic diarrhea of other types

multiple arthritis Other manifestations which have been described are *anemia hypotension* and a generalized skin pigmentation which has suggested the diagnosis of Addison s disease in many cases This seems at first glance to fit well with the disease picture in this patient

It would seem difficult to choose between Whipple s disease and systemic lupus erythematosus Recurrent attacks of fever and arthritis are the key manifestations of the latter and recurrent diarrhea may be a prominent feature This might appear to be a better explanation for the amount of blood loss than Whipple s disease although death

from intestinal hemorrhage has been reported in that disease The abnormalities in absorption are more readily explained on the basis of intestinal lipodystrophy and for this reason the diagnosis of Whipple s disease is preferred

ANATOMICAL DIAGNOSIS (Autopsy No 13858) Ulceration of rectal mucosa Fat accumulation in villi of ileum and in mesenteric lymph nodes with peculiar cellular reaction Chronic infectious arthritis interphalangeal and carpal Rheumatism Rheumatic vegetations on mitral and tricuspid valves Aschoff bodies in myocardium Pericardial adhesions Accessory spleen Pulmonary edema pleural adhesions

The pericardium was roughened by old adhesions The tricuspid valve showed thickening along the line of closure and there were in places distinct nodular elevations Similar lesions were seen along the pulmonary and mitral valves The mucosa of the ileum was dull and granular looking with opaque yellow material between the transverse folds evidently covering the villi The mucosa of the intestine for the greater part of its length showed this same opaque yellow material No distinct ulceration could be seen except in the lower rectum where there were a few small ulcerations

On microscopic examination there was distinct evidence of rheumatic infection in the heart with Aschoff bodies in the myocardium The mitral and tricuspid valve vegetations were typical of rheumatic vegetations with small hyaline masses overlying a tissue composed of rather large elongated cells more or less vertically arranged The cells of the intestinal mucosa were greatly enlarged and contained large fat globules which were doubly refractile and surrounded by a quantity of large mononuclear cells with a granular cytoplasm It was suggested that these might be the lymphatic channels in the villi and the same suggestion was made for the great accumulations of fat in the lymph nodes of the mesentery where they seemed to be surrounded by endothelial cells A striking feature was the presence of giant cells in relation to these fat masses This case corresponded precisely with the syndrome described by Whipple

SUMMARY This 37 year old white male who had attacks of rheumatism for many years three years before admission developed abdominal fullness after eating and watery light colored stools Examination revealed fever skin pigmentation emaciation limitation of movement and swelling of the joints a soft doughy abdomen lymphadenopathy and peripheral edema He had constant diarrhea with frequent bouts of melena He died after passage of a large amount of blood per rectum The stools were grayish in color with the appearance of creamy pus Anemia was progressive The causes of chronic diarrhea were discussed but the usual types could not explain this bizarre clinical picture It was concluded that the illness was probably due to INTESTINAL LIPODYSTROPHY or to an unusual variety of systemic lupus erythematosus Whipple s disease proved to be the correct diagnosis

XIX

(#533482 Admitted May 11 1950 Died May 19 1950)

THIS 62 year old Negro male was admitted because of marked weight loss Five months before entry he first noted that he was losing weight He began to have periods of slight nausea followed by vomiting which usually occurred immediately after a meal He complained of a feeling of tightness in the stomach His appetite diminished and there was considerable eructation Bowel habits were regular and he had no hematemesis melena or jaundice One month before admission he complained of pain in his shoulder and he was thought to have hypertrophic arthritis His weight had decreased 50 pounds by the time of admission and he had become progressively weaker

PHYSICAL EXAMINATION on admission T 98 P 76 R 18 B P 105/65

The patient was a well developed Negro male who appeared weak and lethargic He showed evidence of marked loss of weight He moved about with difficulty due to stiffness of his joints The skin was dry and loose No enlarged lymph nodes were noted There was stiffness and limited range of motion of all joints particularly the shoulders Heberden s nodes were noted on all fingers The pupils reacted normally There was no venous distention The few remaining teeth were carious The tongue showed no atrophy The thyroid was normal in size The lungs were clear to percussion and auscultation The heart was normal in size and rhythm was regular The sounds were distant The abdomen was scaphoid with resistance to palpation There was no abdominal distention and no definite masses could be palpated The liver edge was palpable 3 finger breadths below the costal margin The prostate was three times normal size rubbery and firm with a palpable median bar No hard areas were made out Just above the prostate on the right was an indefinite soft mass the size of which was not determinable The reflexes were equal but hypoactive

COURSE IN THE HOSPITAL The patient ran an irregular fever which was usually most evident after he had been given intravenous fluids He became progressively more lethargic and was obviously disoriented On the third hospital day there was some bleeding from the gums He was incontinent of feces and urine and had trembling of the right arm and mouth By May 17 he no longer responded to verbal stimuli A ventriculogram showed no deformity suggesting a brain tumor Following this he remained in coma moderate stiffness of the neck developed but there were no localizing neurological signs

Laboratory Data Blood serologic test for syphilis was positive with a titer of 1 unit but was negative on a second test On April 12 hematocrit was 44 hemoglobin 14 7 gm leukocyte count 6 000 icterus index 8 sedimentation rate (corrected) 32 mm per hour The differential count on May 14 was 6% juvenile neutrophils 29% segmented neutrophils 7% eosinophils 51% lymphocytes and 7% monocytes The smear was normal Urine showed 5–6 red blood cells and 10–15 white blood cells per high power field no albumin or sugar Stool examination was negative for blood Gastric analysis showed no free hydrochloric acid after histamine On April 25 blood nonprotein nitrogen was 34 mg % total serum protein 8 6 gm % bilirubin 0 8 mg % amylase 237 mg % reducing substance cephalin flocculation 0 thymol turbidity 5 5 units On May 12 the nonprotein nitrogen was 40 mg % CO_2 combining capacity 20 4 mEq/L chloride 102 mEq total serum protein 7 9 gm % with albumin 3 9 gm % On May 15 nonprotein nitrogen was 44 mg % fasting blood sugar 76 mg % phosphorus 4 mg % alkaline phosphatase activity 2 8 units acid phosphatase 1 1 units On May 16 blood calcium was 14 4 mg % On May 18 nonprotein nitrogen was 31 mg % CO_2 combining capacity 26 mEq chloride 85 mEq sodium 129 mEq potassium 4 6 mEq Fluid obtained by lumbar puncture on May 14 was Pandy negative with 1 polymorphonuclear cell per cu mm Wassermann reaction was negative protein was 28 mg % Tuberculin skin test (1st and 2nd strength PPD) negative

An electrocardiogram on May 12 showed normal sinus rhythm a rate of 71 low voltage of the QRS complexes T waves inverted in the 3rd lead and in the V3 lead On April 25 a barium enema showed a large upper sweep to the sigmoid loop Haziness of left lower quadrant within the area of the loop These findings plus the feeling of a resistance in this area indicated the possibility of a mass within the left lower quadrant that was displacing the sigmoid Except for diverticula of the descending colon no intrinsic lesion was seen There were severe hypertrophic changes of the lumbar spine and hip joints There was irregular calcification along the margins of the ilia A repeat barium enema on May 12 showed numerous small diverticula in the descending colon and sigmoid No other evidence of organic bowel lesion was present nor was there abnormality in the terminal ilium A gastrointestinal series revealed a small traction diverticulum in the esophagus The stomach was normal The duodenal cap was asymmetrical and irritable never filling adequately for good visualization No crater was visualized The chest heart and great vessels were within normal limits The lung fields were clear Roentgenogram of the skull showed no abnormalities of the sella base or calvarium On a ventriculogram taken May 18 the lateral ventricles and the third ventricle appeared normal The fourth ventricle was not clearly identified There was extensive calcification within the glomus of both choroid plexuses of the lateral ventricles Some air was in the basal cisterns and there was air in the subarachnoid space about the temporal lobe

Discussion This case illustrates the difficult problem of deciding which of a variety of observations should receive the most em

phasis The history was rather vague It was obvious that the patient had lost weight rapidly and that he had certain gastrointestinal symptoms which might have been produced in the course of a wide variety of diseases There was also a complaint of joint pains There was fever at times and increasing disorientation finally coma There was no appreciable anemia a normal leukocyte count with some increase in eosinophils and lymphocytes The albumin/globulin ratio was inverted and the blood calcium level was 14 4 mg % with a phosphorus level of 4 mg %

One must consider several categories of diseases Despite the presence of some fever the course of this patient s illness does not suggest an infection unless it be tuberculosis Against this are the normal lung fields on x ray and the negative tuberculin tests The rapid progress of the mental difficulties without meningitis would be unusual for disseminated tuberculosis Intestinal diverticula were demonstrated but there were many points against diverticulitis with or without abscess formation

In view of the joint pains cachexia with fever and the eosinophilia one would have to consider periarteritis nodosa This disease has many bizarre clinical patterns and could conceivably fit this picture Renal involvement is not essential but the slowly progressive mental deterioration is not usual and the high blood calcium would be difficult to account for

In the absence of any evidence of rapid skeletal demineralization the quite high blood calcium level is probably a reflection of bony involvement which fits in with the complaint of joint pains without tenderness or swelling The normal phosphorus and phosphatase values rule out hyperparathyroidism there was no history of vitamin D ingestion so that one has left as possibilities for consideration sarcoidosis leukemia multiple myeloma and various neoplasms which may involve bone and lead to an elevation of blood calcium

The high lymphocyte count requires the consideration of leukemia but only briefly Leukemia when unaccompanied by anemia or evidences of leukemic infiltration in lymph nodes or spleen and in which young cells are absent from the peripheral blood would not be expected to run such a rapidly fatal course

One must consider sarcoidosis Lymphocytosis hypercalcemia and inverted albumin/globulin ratio are all frequently seen in this disease However the fatal course and the absence of any evidence of lymph node involvement are rather against this diagnosis

One would be inclined to exclude Hodgkin s disease because of the

absence of any lymph node enlargement or splenomegaly However, this disease also may present bizarre features, and it would not be unusual for the lesions to be confined mainly to bone and abdominal cavity Lymphocytosis and eosinophilia are well known features in many cases and hypercalcemia may occur It would be unusual to see such pronounced nervous system manifestations and also very extensive bony lesions without anemia Monocytoma or lymphosarcoma could produce this clinical picture

Multiple myeloma should always be considered when skeletal pain is present with elevation of serum calcium and globulin With diffuse bony involvement however, there is usually anemia and on careful examination some radiological changes are detectable in most of the cases although not in all With renal involvement there may be elevation of nonprotein nitrogen and mental changes but the nonprotein nitrogen was not consistently elevated in this case and the disorientation and coma would be difficult to account for

This leaves us with some type of neoplasm which may metastasize to the brain and to bone without producing x ray changes and can account for the abdominal manifestations as well Such vague abdominal complaints might have been the result of metastatic lesions in the liver from a tumor originating outside the abdominal cavity

Carcinoma of the prostate seems unlikely from the description of the size and consistency of the gland and the normal serum acid phosphatase value in a case in which metastases would have to be predicted The testicles were normal but a small primary tumor may be overlooked even when extensive metastases have appeared However such metastases usually get to the lung when they are as extensive as they would have to be in this case

Rapid and severe loss of weight suggests pancreatic carcinoma which in this case would have had to be in the body or tail of the pancreas When these tumors spread they almost always seed the peritoneal cavity and ascites results Primary carcinoma of the liver rarely metastasizes to the locations predicted here and tumors of the biliary tract usually produce jaundice before death occurs The x rays led to no suggestion of primary carcinoma of the colon, nor does the clinical picture suggest it in the absence of anemia or intestinal obstruction

The commonest neoplasm in a man of this age is carcinoma of the stomach This diagnosis would account for the vague abdominal symptoms the loss of weight and the absence of free hydrochloric acid from the stomach after histamine stimulation The stool on one

occasion was negative for blood Metastases from a gastric carcinoma may be found in bone and brain but the x ray pictures of the gastro intestinal tract lend no support to this diagnosis although carcinoma of the fundic region cannot be excluded

It seems to me that only one other type of tumor—carcinoma of the lung—need be considered This type of tumor may be accom panied by hypercalcemia without x ray evidence of bony metastases The primary tumor may remain small asymptomatic and not de tectable radiologically Bone pain due to acute pulmonary osteo arthropathy may be the most prominent clinical feature Carcinoma of the lung would explain all the features here if metastases to brain bone and liver were present as they commonly are However it is difficult to account for the blood picture and the elevated serum globulin on this basis The two best possibilities would appear to be carcinoma of the lung and lymphoma

ANATOMICAL DIAGNOSIS (Autopsy No 22418) Tuberculosis adre nals Tubercles in spleen and liver Atrophy and lymphoid infiltration thyroid Aspiration pneumonia Pulmonary edema Acute splenic tumor Urticaria of bladder with eosinophilic infiltration and hemorrhage Fibro ma prostate Hyperplasia of prostate and chronic prostatitis Hypertrophy of bladder Focal scarring and atrophy pancreas Hyalinized islets of Langerhans Diverticula of descending and sigmoid colon bladder and esophagus Moderate atrophy of testis Petechial pleural hemorrhage

One adrenal consisted of a mass of scarring in which calcium had been deposited The other adrenal was large measuring 4 by 2 5 by 7 cm It was composed of dense scar in which yellowish zones of caseous necrosis were present The largest area of necrosis was 2 5 cm in diameter No normal tissue was seen in either adrenal

On microscopic section there was massive tuberculosis of both adrenals Only one small focus of adrenal cells was seen in any of the sections There were scattered tubercles in the spleen and liver but no tuberculosis was evident in the lungs There was atrophy and rather marked lymphoid infiltration in the thyroid There was widespread infiltration with eosino phils throughout the tissues Great numbers of these cells were present between the muscle bundles of the bladder and in the submucosa There was also a blood eosinophilia but in none of the sections were any vascular or collagen lesions seen The bladder was the major seat of the tissue eosinophilia

SUMMARY This 62 year old Negro male had 50 pounds loss in weight anorexia nausea vomiting tightness in the stomach and eructation over a period of 5 months Examination revealed loss of weight weakness lethargy joint stiffness Heberden s nodes resistance to abdominal palpa tion questionable hepatomegaly and prostatic hypertrophy He had fever which was most marked after intravenous infusions He became comatose and died two days after a ventriculogram which was normal He had a

mild eosinophilia and lymphocytosis nonprotein nitrogen was 44 mg % and calcium 14 4 mg % chloride 85 mEq sodium 129 mEq and potassium 4 6 mEq Barium enema suggested a lower quadrant mass displacing the sigmoid The loss of weight and the rapid progress of the illness with coma and death led to a diagnosis of neoplasm The vague abdominal symptoms weight loss weakness mental torpor lymphocytosis hypercalcemia febrile reaction after intravenous infusion and the low sodium and chloride levels in the absence of definite evidence of a neoplasm should have led to the correct diagnosis which was ADDISON S DISEASE DUE TO ADRENAL TUBERCULOSIS

If the advice given in the text of this chapter had been followed in this case it seems probable that the correct diagnosis could have been made

XX

(#192075 Admitted February 2 1940 Died February 28 1940)

THIS 64-year old Negro laborer complained of dyspnea on exertion and swelling of the legs He had done heavy work until 8 months before admission when he first noticed mild dyspnea and ankle edema These became progressively more pronounced Three months before admission he developed urgency and occasional incontinence of urine He complained of weakness of several months duration and had noticed numbness in the ankles with cramping in the legs following walking There had also been numbness and tingling in the fingers of several weeks duration

PHYSICAL EXAMINATION on admission T 98 6 P 100 R 20 B P 130/82

The patient was dyspneic and appeared chronically ill There was pitting edema over the sacrum and buttocks The mucous membranes were pale and on the soft palate small petechial lesions were seen The pupils reacted sluggishly to light The fundi showed no abnormalities The thyroid was not palpable There was no lymph node enlargement There was diminution in resonance at the right lung base The heart was enlarged to percussion the dullness extended 12 cm to the left in the 5th interspace and 4 cm to the right in the 4th interspace The retromanubrial dullness was 7 cm The point of maximal impulse just inside the anterior axillary line in the 5th interspace was well localized and forceful The heart sounds were rapid regular and of normal intensity There was a high pitched systolic murmur at the apex The peripheral arteries were thickened but the pulsations were equal There was no venous engorgement The abdomen was distended and a small amount of free fluid was present An enlarged firm liver was felt with the edge 5 fingerbreadths below the costal margin The spleen was not palpated The prostate was diffusely enlarged but soft Neurological examination revealed no abnormality

COURSE IN THE HOSPITAL The patient improved rapidly on rest in bed and the shortness of breath and edema almost disappeared before he was digitalized The liver however did not decrease appreciably in size A marked anemia was noted and the nonprotein nitrogen of the blood became progressively elevated starting at 84 mg During the second week in the hospital bleeding from the gums developed An irregularity of the pulse which was thought to be due to extrasystoles was noted On the day of death about two hours after a cystoscopic examination he developed pain in the epigastrium and became short of breath The pulse rate was elevated and the pulse feeble The blood pressure fell to 60 40 The heart sounds were distant and death occurred within a few hours

Laboratory Data Blood serologic test for syphilis was negative hemoglobin 11 gm hematocrit 31 Leukocyte count was 7 440 with 4% myelocytes 74% polymorphonuclear cells 2% eosinophils 1% basophils 4% monocytes and 15% lymphocytes Smear showed no abnormalities the platelets were numerous Blood nonprotein nitrogen was 84 mg% sugar 124 mg% CO_2 combining power 44 7 vol% total proteins 5 4 gm% chlorides 111 2 mEq calcium 10 2 mg% phosphorus 6 6 mg% Urine had a specific gravity of 1 011 to 1 016 albumin was present in large amounts on occasions some leukocytes occasional casts and a few red blood cells were present in the sediment The phenolsulfonphthalein test of kidney function showed less than 5% excretion in two hours Urine cultures no growth Venous pressure 70 mm of saline Urological consultant found prostatic hypertrophy A retrograde pyelogram was done on the left which showed a normal kidney with some dilatation of the lower ureter Changes were noted in the lower lumbar vertebrae and in the left ileum which suggested the possibility of bone metastases Stools negative for blood and parasites

Roentgenographic examination on February 2 showed the heart enlarged to the left aorta normal lungs clear On February 10 a barium enema revealed no evidence of neoplasm X ray of the stomach on February 12 showed no organic lesion in the upper gastrointestinal tract On February 21 there was a small area of radiolucency in the left side of the skull which did not have the typical appearance of a metastatic lesion There was no evidence of metastases in the long bones or spine Electrocardiograms on February 3 revealed normal sinus rhythm P R interval prolonged (0 26 sec) T1 was upright but low T2 T3 T4 and T5 were inverted Changes were possibly due to digitalis On February 19 there were normal sinus rhythm partial heart block with prolonged P R interval (0 24 sec) and an occasional dropped beat T1 was biphasic T2 inverted and T3 inverted

Discussion The three outstanding features to be explained are (1) the cause of the myocardial insufficiency (2) the persistent hepatomegaly after the heart failure subsided and (3) the cause of the progressive renal failure in the absence of any hypertension

For practical purposes (as described earlier) one may place the causes of cardiac insufficiency in six main categories

(1) Failure following valvular disease,
(2) Failure following systemic hypertension
(3) Failure following hypertension in the pulmonary circulation
(4) Failure following pericardial disease
(5) Failure associated with congenital defects, and
(6) Failure due to disease of the myocardium

A systolic bruit was audible but such is almost always the case when the heart is enlarged and it does not necessarily indicate disease of the mitral valve In addition a systolic murmur is almost always

present in a patient with this degree of anemia In the absence of more significant auscultatory evidence it seems altogether unlikely that this man had valvular heart disease At no time was his blood pressure elevated and the clinical picture was not that of hypertension in the lesser or pulmonary circulation There was no fact in the history or in the physical examination to suggest disease of the pericardium or any congenital defect Thus there must have been some type of myocardial disease In a man of this age who had evidence of peripheral arteriosclerosis the most probable cause would be coronary arteriosclerosis but let us leave a final decision until we have looked at the other important features of the case

There are three major groups of diseases which may lead to uniform enlargement of the liver

(1) Chronic passive congestion or venous obstruction
(2) Obstruction to bile duct outflow of a persistent type
(3) Conditions producing diffuse or generalized changes in the liver parenchyma

The conditions in group 1 can be readily eliminated as the liver size did not decrease as the signs of congestive heart failure including the dependent edema and ascites disappeared All of the conditions in Group 2 are accompanied by jaundice which was never present

In the third group one may list as possibilities

(a) Cirrhosis of the liver
(b) Hodgkin s disease or leukemia
(c) Sarcoidosis
(d) Primary or secondary neoplasm
(e) Amyloidosis

One would not expect such great enlargement in Laennec s cirrhosis unless it was in the early stage with fatty infiltration This diagnosis would be coincidental since it would not explain the other manifestations It is rare to have massive enlargement of the liver with Hodgkin s disease leukemia or sarcoidosis in the absence of enlargement of the spleen or of the superficial lymph nodes Again none of these possibilities except sarcoidosis would serve to explain the renal picture Other evidences of sarcoidosis were not present Primary carcinoma of the liver rarely causes massive and at the same time uniform enlargement of the liver Again the cardiac and renal manifestations would have to be explained on another basis With such great enlargement of the liver from metastatic carcinoma one would expect to feel some irregularities in its surface Furthermore no primary tumor which could serve as a source of metastases was

located although numerous x ray examinations were made Having only one possibility left to explain the hepatomegaly namely amyloidosis let us now consider the possible causes of the renal insufficiency and progressive uremia

In view of the rapid progress of the uremia in the absence of obstruction to the lower urinary tract, and the finding of large amounts of albumin and some casts and red cells in the urine I believe that we are dealing in this case with a disease which affects the kidneys diffusely This may prove to be either

(1) Arteriolosclerotic nephritis
(2) Glomerulonephritis or
(3) Amyloidosis

It is unusual for arteriolosclerotic nephritis or chronic glomerulonephritis to reach such an advanced stage of renal insufficiency without hypertension On the other hand it is characteristic of amyloid infiltration to produce renal insufficiency with marked albuminuria and no elevation of blood pressure so called *amyloid nephrosis* This diagnosis would also fit well with the diffuse enlargement of the liver which did not lessen when the dyspnea and edema subsided There was no evident chronic infection or other obvious cause for secondary amyloidosis and so called primary amyloidosis is rare Let us, however make a tentative diagnosis of primary amyloidosis and see if it provides an adequate explanation for all the facts

In *primary amyloidosis* there may be deposits in tissues other than those commonly involved in the secondary ordinary type associated with chronic infections In the latter the kidney liver, and spleen are most often affected In the primary type the heart muscle may also be invaded leading to heart failure In the present case we have concluded that his cardiac difficulty was myocardial in origin One could therefore explain all three of the major features of this case on the basis of one diagnosis—

Amyloidosis with involvement of the cardiac muscle the liver and the kidneys

This leaves us with one feature still unexplained—his *sudden death* If trauma and poisoning can be excluded as they can be in this case it is statistically probable that he died either of sudden failure of the heart hemorrhage or arterial embolism or thrombosis In many instances autopsy fails to reveal any cause of sudden death and one assumes that ventricular fibrillation was responsible It might well be that ventricular fibrillation occurred in this case as a result of amyloidosis of the heart However the final episode with sudden pain in

the epigastrium and a precipitous fall in blood pressure suggests very strongly that he had a coronary occlusion This was probably not a complication of amyloidosis Coronary occlusion in a man of this age without syphilis is almost always due to coronary arteriosclerosis However in spite of the fact that this seems the most likely cause of the terminal event the course of the final illness beginning 8 months before death cannot be satisfactorily explained on the basis of arteriosclerotic cardiac and renal disease alone Accordingly my final diagnosis is primary amyloidosis

ANATOMICAL DIAGNOSIS (Autopsy No 16815) Amyloid deposits in liver spleen kidneys adrenals heart bladder thyroid pancreas prostate seminal vessels and in small arteries and terminal arterioles in most tissues including intestine and hypophysis Focal lipoid deposits in arterioles in kidneys pancreas adrenals and heart (hyaline arteriolosclerosis) Cardiac hypertrophy and dilatation Adenomas of prostate Arteriosclerosis and stenosis of coronary arteries Emphysema Pulmonary edema

The heart was large and the myocardium very firm The right side was dilated and the muscle hypertrophied. The endocardium of the right and left auricles showed a fine granular roughening in patches These granules were like grains of sand and were slightly yellow This appearance was characteristic of amyloid deposits and when iodine and sulfuric acid were applied all of them turned black Similar black foci developed when these solutions were applied to the myocardial area There was a fairly well marked patchy sclerosis of all the coronary arteries and at several points there was marked narrowing of the right the left anterior descending and the circumflex arteries The liver was large and hard and had a pale translucent glassy appearance The lobulation was indistinct The spleen was enlarged and extremely hard also having a glassy translucent appearance The pancreas was firmer than usual and again application of iodine and acid showed many black areas The kidneys were normal in size and appeared a little roughened The striations were fairly well preserved and the cortex was not much reduced in width Application of the iodine and acid showed many black lines in the cortex and black foci apparently glomeruli but the pyramids appeared to be free from amyloid Amyloid was also present in the thyroid On microscopic examination there were widespread amyloid deposits No cause was found for the amyloidosis In the heart the amyloid was found in the walls of the small arteries and in patches between the muscle fibers

SUMMARY This 64-year old Negro laborer developed progressive dyspnea and edema 9 months before death He appeared chronically ill with dyspnea peripheral edema pallor cardiomegaly hepatomegaly ascites and prostatic enlargement There were anemia azotemia albuminuria and reduced phenolsulfonphthalein excretion The patient developed bleeding from the gums and extrasystoles were noted After cystoscopy he developed epigastric pain and hypotension dying a few hours later Changes noted in the x rays of the left ileum suggested metastases The

three major features to be explained were (1) the cause of cardiac insufficiency (2) the hepatomegaly which persisted after the heart failure subsided and (3) the progressive renal failure without hypertension Analyses of the possible causes of the three manifestations suggested that the entire picture could be explained by one diagnosis PRIMARY AMYLOIDOSIS This diagnosis was confirmed at autopsy

XXI

(#492212 1st admitted August 25 1950 to November 4 1950
Re admitted December 19 1950 Died December 20 1950)

THIS 71 year old white woman first entered the hospital because of 40 pounds loss in weight A widow she had been living alone for 11 years subsisting on a small pension She was reasonably well until 8 months before admission when she developed epigastric pain after eating solid foods and occasional episodes of nausea and vomiting She lost weight and grew weaker abstaining from solid foods because of the epigastric discomfort There was no anorexia By three months before entry she had lost 30 pounds in weight and the epigastric pains were worse She complained of thickness of her tongue and inability to swallow solid foods After taking cod liver oil she developed diarrhea which was intermittently present with several stools daily until admission

PHYSICAL EXAMINATION on first admission T 99 P 70 R 20 B P 110/70

The patient was cachectic and garrulous The skin was warm moist and loose No pigmentation or eruption was noted The mucous membranes were dry and pale The eyes were normal except for bilateral lenticular opacities The patient was completely edentulous The tongue was red and atrophic along the margins There was cheilosis bilaterally The pharynx was reddened There was no general or localized adenopathy The thyroid was not enlarged The breasts were normal The lungs were clear The precordium was quiet and the heart normal in size A blowing systolic murmur was described The peripheral vessels were sclerotic There was no abdominal distention or tenderness No organs or masses were palpated Several small lumps were felt in the lower quadrants thought to be fecal material Pelvic examination revealed no abnormalities No masses were felt on rectal examination The extremities showed marked muscular wasting There was pitting edema of the legs Vibratory perception was impaired over the lower extremities and the deep reflexes were diminished

COURSE IN THE HOSPITAL. The patient had a macrocytic anemia without bone marrow changes characteristic of pernicious anemia and her serum albumin level was low No specific lesion could be found to account for the abdominal symptoms She was placed on vitamin B_1 There was a reticulocyte response to 6 per cent but the hematocrit continued to fall until transfusions were given Throughout her stay anorexia was severe it was difficult to get her to eat and at times she was intubated for proper nutrition She was placed on intensive vitamin therapy There

had been little improvement however at the time of her discharge on November 4

Laboratory Data At the time of the first admission on August 25 red blood cell count was 3 25 million hemoglobin 10 gm hematocrit 36 icterus index 5 sedimentation rate (corrected) 18 mm per hour mean corpuscular volume 100 mean corpuscular hemoglobin 33 mean corpuscular hemoglobin concentration 28 cells normal size good color Total leukocyte count was 15 000 with 35% juvenile neutrophils 60% segmented neutrophils 2% lymphocytes and 3% monocytes

During the first admission the hematocrit value fell to 28 Transfusions were given and the patient was discharged with hematocrit 44 The leukocyte count came to normal in the hospital Urine had a specific gravity of 1 014 slight trace of sugar albumin 0 few white blood cells and a rare cast Urine culture showed growth of A aerogenes and alpha streptococcus Phenolsulfonphthalein test showed 52% excretion in 2 hours *Stool examinations were negative for blood and parasites Stool* cultures on one occasion showed growth of Salmonella organisms Fecal urobilinogen was less than 50 Ehrlich units

On August 25 blood nonprotein nitrogen was 42 mg % CO_2 combining capacity 22 5 mEq chloride 100 5 mEq sodium 139 6 mEq total serum protein 5 1 gm % with 1 7 gm % albumin cholesterol 80 mg % serum calcium 8 1 mg % phosphorus 2 mg % alkaline phosphatase activity 4 2 Bodansky units In the hospital the nonprotein nitrogen fell to 24 mg % the cholesterol rose to 160 mg % and the albumin to 2 9 gm % Gastric analysis showed no free hydrochloric acid after histamine The basal metabolic rate was plus 1

Fluid removed from the right chest showed specific gravity of 1 004 with a total cell count of 960 per cu mm Gastric washings were cultured but no tubercle bacilli were found

Electrocardiogram on August 25 showed normal sinus rhythm low voltage sagging ST1 ST2 and ST3 with staircase T waves Q T interval prolonged T waves were of the type seen in hypokalemia

A gastrointestinal series on August 19 showed a normal esophagus The stomach had an S shaped antrum which appeared narrower than normal However peristalsis passed through this region and no definite evidence of a lesion was seen The duodenal bulb filled well Just distal to the ligament of Treitz there was a small loop of dilated jejunum partially filled with barium The possibility of intussusception was suggested No definite obstructive changes were seen proximal to this point Some calcification was noted probably in the lymph nodes

On August 25 with barium enema the entire large bowel filled well and appeared normal

On September 25 chest x ray showed bilateral pleural effusion There did not appear to be any parenchymal infiltration in either lung

Subsequent Course On December 12 1950 the patient returned stating that she had had a cold for 7 days with expectoration of yellowish green sputum There was dullness with suppression of breath sounds at the right base and rales were noted at the left base The legs were edema

tous She was put on digitalis X ray examination of the chest at this time showed the right lower lung field was obscured by an extensive pleural reaction with effusion The left lung appeared grossly normal except for a rounded density extending outward from the hilus in the mid lung field There was no definite evidence of pneumonitis

The patient returned on December 19 complaining of pain in the right chest At that time she was cyanotic and dehydrated

PHYSICAL EXAMINATION on second admission The temperature was subnormal and the blood pressure was unobtainable The patient was semicomatose and very cachectic The tongue was dry and red There was dullness at the right lung base up to the midscapular region and rales at the left base The heart sounds were distant There was edema of the abdominal wall No masses or organs could be palpated Pitting edema of the ankles was noted The deep reflexes were unobtainable

COURSE IN THE HOSPITAL After administration of oxygen and plasma the patient became oriented and developed distention of the neck veins However she soon became less alert and died the following day

LABORATORY DATA Hemoglobin 9 gm Urine showed a trace of albumin and an occasional white cell

DISCUSSION The only finding about which this diagnostic problem can be approached systematically is the macrocytic anemia Apparently there was no distinct megaloblastic change in the bone marrow and although the patient had a fairly good reticulocyte response to vitamin B_{12} there was no rise in the hematocrit The leukocyte count was never low and the platelets were not recorded as being abnormal

Pernicious anemia is of course a possibility There was evidence of gastrointestinal and nervous system involvement and there was achlorhydria even after histamine However the absence of a megaloblastic marrow and the poor response to vitamin B_{12} are strongly against this diagnosis The response to vitamin B_{12} may be poor in elderly patients and in those who have infections Nevertheless I believe that this was not true pernicious anemia

The symptomatology of non tropical sprue qualitatively resembles that of pernicious anemia but again a more adequate response should have followed the intensive therapy

The mental changes here are probably consistent with the patient s age and the degree of anemia However with the diarrhea and story of poor nutrition pellagra must be considered The anemia of pellagra is usually not severe but it may be macrocytic The absence of dermatitis and the poor response to treatment would tend to rule out pellagra

Macrocytic anemia occurs in association with disease of the liver

It is usually only moderate in degree A clear cut response to therapy with liver extract is not usually observed There was no jaundice or ascites and although there was hypoproteinemia and edema, the liver was never enlarged No liver function studies were done but I doubt if primary liver disease need be seriously considered

The picture of pernicious anemia may be closely simulated by a variety of diseases which produce stasis in the gastrointestinal tract The symptoms are frequently those of partial intestinal obstruction with marked loss of weight These patients may have glossitis and neural involvement occurs in about 10 per cent This syndrome was first described by Faber in 1895 under the title Pernicious Anemia with Stricture of the Small Intestine Most of these cases show a response to treatment with liver extract even before surgical removal of the defect particularly if it is a single stricture or a blind loop A variety of pathological conditions have been found as the basis for the partial obstruction in these cases The stricture may occur in the jejunum the ileum or the ascending transverse or descending colon The cause may be tuberculosis stenosing regional ileitis or colitis adhesions neoplastic growth stasis in multiple diverticula or a large Meckel s diverticulum The strictures occur most commonly in the ileum and about one third are due to tuberculosis

The x ray studies in the present case seem adequate to rule out diffuse disease of the gastrointestinal tract On the other hand both the symptoms and the x ray findings are compatible with an obstructive lesion of the small bowel The calcific deposits in the abdomen may be in old tuberculous nodes and this picture could readily be due to small bowel tuberculosis Neoplasm however, is difficult to rule out in view of the poor response to therapy The late appearance of the pleural effusion even though the fluid had the characteristics of a transudate might favor tuberculosis If the patient had a carcinoma of the colon with diarrhea, one would have expected to find blood in some of the numerous stool examinations Macrocytic anemia has been described in cases of hypothyroidism but there is no reason to suspect myxedema in this case

The most likely diagnosis seems to be stricture of the jejunum due to tuberculosis The questionable lesion noted in the x ray studies might well have been the result of a tuberculous stricture

ANATOMICAL DIAGNOSIS (Autopsy No 22776) Calcification of gastrohepatic lymph nodes Calcified focus in hilar node Tuberculous enteritis with stricture and partial obstruction Right and left organized and organizing pulmonary thrombi with infarction of right middle lobe Right

pleural effusion and pulmonary edema Aspiration lobular pneumonia Ascites and dependent edema Patchy fibrous pleuritis right apex and obliterative fibrous pleuritis left Chronic pyelitis and necrosis of renal papillae Generalized arteriosclerosis particularly of cerebral arteries Marked cachexia Extreme fatty infiltration of liver Necroses in hypophysis

The coronary arteries were partially calcified and there was narrowing of the right coronary artery The aorta was sclerotic and the abdominal portion rigidly calcified There was a sharply demarcated area at the anterior basal margin of the middle lobe of the right lung which was the site of a large cavity There were thrombi in many small vessels at the hilum of this lobe The spleen as well as the liver contained a number of tiny calcified nodules A segment of intestine about 40 cm long in the region of the lower jejunum had a markedly stenosed lumen due to a deep irregular ulceration which encircled the bowel Branching septa of mucosa bridged this ulcer The proximal limb of this segment was dilated and its muscle hypertrophied In the dilated portion there were irregular deep ulcerations of the mucosa Some mesenteric nodes nearby contained small firm nodules but no tubercles were seen on the serosal surfaces The distal segment of this limb was normal in appearance

Microscopically the region of the ulcerated lesions showed caseous necrosis and there were tubercles as well in which acid fast bacilli were stained It would appear then that the disease which was producing the signs and symptoms in this individual was tuberculous enteritis

SUMMARY Eight months before admission this 71 year old white woman developed nausea vomiting and epigastric discomfort after taking solid food With reduced food intake she lost weight and grew weaker and five months later noted the onset of dysphagia and intermittent diarrhea She was cachectic and pale The tongue was red with marginal papillary atrophy There was peripheral arteriosclerosis pitting edema impairment of vibratory perception and diminished deep reflexes in the lower extremities A macrocytic anemia without megaloblastic changes in the bone marrow was found The serum albumin level was low A leukocytosis with shift to the left was present No cause was found for the abdominal complaints and the patient responded poorly to therapy which included vitamin B_1 She was discharged from the hospital at the end of 10 weeks but 6 weeks later returned with a productive cough signs at the right lung base and pain in the right chest She was semicomatose cachectic and edematous In the gastrointestinal series a small dilated loop of jejunum was noted The various causes of macrocytic anemia were discussed The cachexia and the manifestations suggesting partial intestinal obstruction as well as the finding of a small dilated jejunal loop were in favor of benign stricture of the small intestine possibly due to tuberculosis as the basic lesion Autopsy revealed TUBERCULOUS ENTERITIS WITH JEJUNAL STRICTURE and partial obstruction

XXII

(#403933 Admitted November 13, 1946
Died November 29, 1946)

THIS 58 year old white male was admitted because of abdominal cramps and persistent diarrhea Eight years previously, he developed epigastric pains of a gnawing burning character which appeared two or three hours after meals and were promptly relieved by food He had had these symptoms intermittently for three years when he had an acute perforation of a peptic ulcer A duodenal ulcer was excised and a posterior gastroenterostomy performed For the following year he got along well Four years before admission pain began to recur In 1944 two years before admission a severe gastrointestinal hemorrhage necessitated several blood transfusions Then except for occasional bouts of diarrhea and abdominal pain he felt well until two months before admission, when he suddenly began to have uncontrollable diarrhea There was extreme urgency as well as inability to control the bowel movements Crampy pains in the lower abdomen accompanied the diarrhea and undigested food was passed by rectum within six to eight hours after ingestion He lost weight rapidly Three weeks before admission he developed edema of the ankles and legs and felt weak and fatigued He averaged thirteen bowel movements per day The cramping pains began two or three hours after eating in the region of the hepatic flexure and moved along the course of the colon Bowel movements gave considerable relief of pain

PHYSICAL EXAMINATION on admission T 98 6 P 70 R 20 BP 96/65

The patient was chronically ill and cadaveric in appearance The skin was loose and inelastic There was no lymph node enlargement The pupils reacted normally There was complete edentia The tongue was normal The thyroid was not enlarged The lungs were clear to percussion and auscultation The heart was normal There was slight thickening of the peripheral vessels The abdomen was distended There was a slight herniation through the operative scar No tenderness or spasticity was noted The liver and spleen were not enlarged There was no evidence of ascites Rectal examination was negative There was moderate edema of the lower legs Neurological examination showed no abnormalities

COURSE IN THE HOSPITAL The patient was placed on a high protein high-calorie diet with vitamin supplements much of the nourishment being given intravenously in the form of protein hydrolysate and glucose There were occasional slight elevations in temperature His stools decreased in

number and during the second week he went five days with no stool passage reported The edema disappeared and except for occasional vomiting he seemed to be improving and was being prepared for operation when he suddenly died

LABORATORY DATA Red blood count was 4 37 million hemoglobin 11 3 gm hematocrit 35 icterus index 2 sedimentation rate 0 leukocyte count 9 000 with 80% polymorphonuclear cells 1% eosinophils 17% lymphocytes and 2% monocytes Smear showed slight hypochromia but no other abnormalities Blood serologic test for syphilis negative Urine examination normal

Blood nonprotein nitrogen was 29 mg % fasting blood sugar 72 mg % CO_2-combining power 23 7 mEq chlorides 107 9 mEq serum albumin 2 81 gm % globulin 1 88 gm % cholesterol 70 mg % calcium 8 4 mg % Cephalin flocculation test was negative Prothrombin time 21 seconds (75% of normal) Bromsulfalein test 15% retention in 30 minutes Phenol sulfonphthalein test showed 18% excretion in 15 minutes 32% 1 hour 8% 2 hours total 58% Cultures of the stools showed no pathogenic organisms No abnormal lesions were seen on gastroscopic or sigmoidoscopic examinations

Flat plate of the abdomen showed localized dilatation of the loops of bowel on the right side of the abdomen On fluoroscopic examination it was demonstrated that the stomach emptied itself through the stoma and the pylorus The duodenal bulb was deformed There appeared to be a fistulous communication between the small intestine and the large probably the transverse colon on the right side However this could not be demonstrated in any of the films Barium appeared in the splenic flexure at the end of three hours Extensive areas of the small intestine had an abnormal appearance There was evidence of partial obstruction of the small bowel Barium enema showed a normal large intestine

DISCUSSION The sequence of events in this case—the history of duodenal ulcer with perforation excision and posterior gastroenterostomy followed by massive intestinal hemorrhage and then the development of persistent severe diarrhea and a demonstrable enterocolic fistula—seems superficially to leave little doubt as to the nature of the patient s illness The obvious conclusion is that he developed a marginal or jejunal ulcer which perforated into the transverse colon His sudden death might have been due to sudden massive intestinal hemorrhage or to a pulmonary embolus since phlebothrombosis is not infrequent in chronically ill bed ridden patients

However certain features lead one to believe that other possibilities must be considered The vomitus was never described as fecal in character undigested food was said to have been observed in the stool but only after 6 to 8 hours despite the fluoroscopic report no passage of barium from the small to the large bowel could be demonstrated in any of the x ray films striking x ray changes were noted

only in the small bowel Such extensive and bizarre changes in the intestines are more likely the result of some intrinsic disease rather than of simple nutritional deficiency An added fact is that there was evidence suggestive of involvement of the liver Nutritional deficiency may have accounted for the very low blood cholesterol and the slight retention of phenolsulfonphthalein, but the possibility must be kept in mind that the liver might be involved in some disease process This could conceivably be a case of inadvertent gastro ileostomy but the long time interval after operation and the long period of freedom from symptoms make it unlikely

Now if one chooses to ignore the obvious implication of the duodenal ulcer with all of the events which followed naturally in its train what other conditions can be suggested? (See Table 27 for list of causes of chronic diarrhea) Specific diffuse lesions of the small bowel are rare Tuberculosis may cause such lesions but usually only in the late stages when extensive pulmonary tuberculosis is present There is no evidence to support the diagnosis of tuberculosis in this case Granulomatous lesions which have been designated as regional enteritis may on occasions be extensive and involve multiple areas of the ileum and jejunum Relatively stenotic areas and loops of dilated small bowel may be seen and a tender mass (or masses) is usually present The diarrhea is usually not as severe as in this case and there is a low grade irregular fever which was not present here Difficult to distinguish from so called regional ileitis is disseminated lympho

Table 27 Causes of Chronic Diarrhea

I Infections
- A Dysentery
  - 1 Bacillary
  - 2 Amebic
- B Typhoid fever
- C Generalized infection
- D Staphylococcal (toxin)
- E Malaria
- F Lymphogranuloma venereum
- G Mycobacterial
  - 1 Local infection
  - 2 Secondary to cavitary pulmonary tuberculosis
- H Fungi
- I Other parasitic diseases

II Local non specific inflammatory diseases
- A Regional ileitis

- B Ulcerative colitis
- C Diverticulitis
- D Extrinsic lesion with reflex diarrhea

III Metabolic and chemical
- A Chemical poisons
  - 1 Arsenic
  - 2 Mercury
- B Cholinergic drugs
- C Hyperthyroidism
- D Addison s disease
- E Hypoparathyroidism
- F Diabetes (autonomic nervous system?)
- G Cathartics habitual
- H Uremic colitis
- I Intestinal lipodystrophy (Whipple s disease)
- J Amyloidosis
- K Deficiency states
  - 1 Achlorhydric
  - 2 Vitamin deficiencies
    - a Pellagra
    - b Sprue
    - c Pernicious anemia
- L Chronic pancreatitis
- M Biliary obstruction

IV Neoplasms and granulomatous disease
- A Carcinoma of colon or rectum
- B Polyposis
- C Hodgkin s disease lymphosarcoma sarcoidosis
- D Leukemia
- E Carcinoma of pancreas
- F Carcinoma of stomach
- G Other

V Other
- A Circulatory
  - 1 Chronic passive congestion
  - 2 Portal obstruction
- B Allergy (food)
- C Emotional
- D Gastrocolic fistula
- E Partial obstruction
- F Inadvertent gastro ileostomy
- G Post gastrectomy
- H Connective tissue diseases
  - 1 Periarteritis nodosa
  - 2 Systemic lupus erythematosus

sarcomatosis of the small bowel This may occur in the absence of any other clinically recognizable lesion of the disease and would I believe be expected to produce the type of x ray picture which was demonstrated in the small intestine of this patient It is worth recalling that this man had occasional attacks of diarrhea and abdominal pain for over a year before the more severe manifestations began It is not inconceivable if the fluoroscopic impression was correct that this type of lesion could produce an enterocolic opening and in addition could explain the rather meager evidence suggestive of hepatic involvement The final diagnosis is lymphosarcoma

COMMENT In retrospect this man had complained of severe weakness and had severe diarrhea of moderately long duration In spite of the fact that reflexes were obtained on admission it seems entirely possible that his sudden death was associated with a potassium deficiency which was aggravated by the intravenous administration of saline and glucose without added potassium (Added 1954)

ANATOMICAL DIAGNOSIS (Autopsy No 20286) History of gastro enterostomy for duodenal ulcer 5 years before death Gastro ileostomy 20 cm above ileocolic valve Stenosis of distal limb at anastomosis Dilatation and hypertrophy of ileum above anastomosis Generalized arteriosclerosis with arteriosclerotic aneurysm of abdominal aorta Scarring of left ventricular myocardium Central atrophy of liver Pleural scars in apices of both lungs

The duodenum ended blindly in its lower portion There was a puckered gastro enterostomy orifice completely healed and covered with smooth mucosa This led to a loop of gut the short end of which was thick walled and dilated and the longer loop of which was normally delicate with a normal lumen There were scarring and adhesions about the outer surface of the thickened portion of the loop of the anastomosis The ileocecal region had been sutured The loop of ileum used was evidently the terminal one for the anastomosis which was a side to side one at a level only 20 cm above the ileocecal valve The dilatation of the small bowel begin on the proximal side of the anastomosis and extended throughout the abdomen being filled with dilated loops

The cause of the sudden death was not clear although examination of the coronary arteries showed that they were markedly narrowed by sclerosis in numerous places but nowhere occluded

SUMMARY This 58 year old man 8 years before admission developed a duodenal ulcer which perforated after three years was excised and a gastro enterostomy was performed Four years before admission pain recurred and 2 years later he had a massive gastrointestinal hemorrhage He was then well except for occasional bouts of pain and diarrhea until two months before entry when severe crampy pain and uncontrollable diarrhea developed Examination revealed a chronically ill cachectic man who was edentulous and had abdominal distention There was mild

anemia X ray showed a fistulous communication between the small and large bowel *and evidence of extensive involvement of the small intestine* With intravenous alimentation the diarrhea and edema improved greatly Then he suddenly died The sequence of events seemed compatible with a marginal ulcer with development of an enterocolic fistula or inadvertent gastro ileostomy The course of the final illness and the x ray findings *raised the question of a superimposed disease capable of producing diffuse* involvement of the small bowel Accordingly a diagnosis of lymphosar coma was made Autopsy revealed that an INADVERTENT GASTRO-ILEOSTOMY had been performed and that its stoma was only 20 cm above the ileocecal valve

XXIII

(#272477 Admitted October 24 1952 Died November 24 1952)

THIS 68 year old diabetic entered the hospital complaining of loss of 20 pounds in weight and burning on urination for 2 months Previous examination had revealed an enlarged rubbery prostate with residual urine of 275 ml so he was admitted for treatment of his diabetes and for a prostatectomy

His mother had died of diabetes His own diabetes had been discovered in 1942 but he had not followed a special diet During the two years following the discovery of the diabetes he had had polydipsia polyphagia and weakness and had lost 40 pounds in weight He had developed an infection of his hand in 1945 following which he became acidotic and was admitted to the hospital for treatment At that time he had a normal temperature The blood pressure was 160/90 Respirations were deep and rapid CO combining power was 6 9 mEq /L and the blood sugar 478 mg % The infected hand was incised and he was treated with penicillin At the time of discharge he was on a diet and taking regular insulin 20 units daily He was followed until December 1949 after which he failed to return At that time he was on a diet and was taking protamine zinc insulin 8 units daily He returned in October 1952 complaining of weight loss of 20 lbs and dysuria He stated that he had been taking 10 units of protamine insulin daily

PHYSICAL EXAMINATION on admission Blood pressure was 150/100 There was evident weight loss The liver was palpable one fingerbreadth below the costal margin The prostate was greatly enlarged

LABORATORY DATA The urine contained 4 plus sugar and an occasional white cell was seen on microscopic examination The urological consultant found 275 ml of residual urine and thought the patient should have a prostatectomy On admission the nonprotein nitrogen was 35 mg % sugar 293 mg % CO_2 combining power 27 mEq chlorides 101 mEq Table 28 lists the chemical findings and the insulin dosages throughout *the patient s stay in hospital with other remarks on condition* and treatment

COURSE IN THE HOSPITAL The patient s blood sugar reached normal levels and on November 5 under spinal anesthesia a perineal prostatectomy was performed There was no difficulty during the procedure and the microscopic specimens revealed only prostatic hyperplasia

Following the operation a transfusion of 500 ml of whole blood was given It was noted on this day that the patient had several shaking chills

Table 28 Chemical Findings

Date	BLOOD				FLUID		Remarks
	NPN mg /	Sugar mg /	CO_2 mEq	Chloride mEq	In take	Out put	
10/25/52	35	293	27 0	101 0	1310	950	PZI 15 units
10/28/52		240			2700	1350	PZI 15 units
10/29/52		208			3385	900	PZI 15 units CZI 25 units
10/30/52		220			3120	2300	PZI 25 units
11/1/52		162			3630	2000	PZI 25 units
11/3/52		147			3330	2350	PZI 25 units
11/5/52							Perineal prostatectomy done
11/6/52		255			2640	1400	PZI 25 units Severe wound infection 900 000 units penicillin 1 gram streptomycin
11/8/52		320			6500	1350	Severe acidosis PZI 35 units Antibiotic contin ued Wound still infected
11/9/52		250			2965	2150	I ZI 55 units Penicillin 900 000 u Acidosis now improving
11/10/52	57	262	25 8	94 5	3870	1670	Infection improving PZI 55 units Penicillin 900 000 u
11/11/52		220	27 6		2965	2150	I ZI 55 units
11/12/52		162			2790	1500	PZI 45 units Penicillin 900 000 *units*
11/13/52		104			2475	1800	PZI 35 units
11/15/52		84			2530	2700	PZI 15 units Penicillin 900 000 units
11/17/52		130			2095	2250	PZI 0 Penicillin 900 000 u
11/19/52		117			2570	1975	PZI 0 Penicillin 900 000 units
11/20/52					2065	2950	PZI 0
11/21/52		no glycosuria			3570	2700	Pen 900 000 u *PZI 0*
11/22/52					5740	1675	Pen 900 000 u PZI 0
11/23/52					5300	2000	Pen 900 000 u PZI 0
11/24/52							PZI 0

On November 7 serosanguinous fluid and air was expressed from the incision On November 10 the patient was allowed to be up there was no incisional drainage and the urine was clear On November 11 a note was made that it was difficult to understand that he had no sugar in his urine at 7 00 A M while at 11 00 A M the test for sugar was 3 plus although he was on a carefully controlled diet and was getting morning insulin It was thought that he might be receiving some food from outside the hospi tal During this period he was receiving about 35 units of protamine zinc

insulin On November 13 it was noted that the incision was healing poorly and showed a moderate drainage of pus On that day the urine sugar was 0 for the 24 hour period The following day the urine was found to have 25 to 40 white blood cells per high power field in an uncentrifuged specimen and the wound was draining purulent material The urine was foul smelling and fecal contamination was suspected The blood sugar on November 15 was 84 mg % A medical consultant saw the patient on November 24 The chief findings of his examination were recorded as follows The patient has needed no insulin for several days He has been vomiting Following intravenous fluids on November 24 he suddenly became unconscious and drooled with twitching of the eyes orbicularis oculi and other facial muscles Temperature was 102 Pulse 120 Respirations 16 They were deep and noisy He was comatose and responded only slightly to painful stimuli The neck was stiff Blood pressure was normal Examination of the extremities revealed flaccidity on the left There was ankle clonus bilaterally which was not well sustained The abdominal reflexes could not be elicited There was twitching of the left pectoral muscles

It was thought that the patient had had a cerebral vascular accident with possibly a subarachnoid hemorrhage It was stated that the event might be related to hypoglycemia The patient died a few hours later The blood chemical examinations on the day of death were not made available to the discusser Blood cultures were sterile

An ophthalmological consultant had seen the patient on November 21 for pain over the eyes and back of the head for four or five days Examination revealed attenuated retinal arteries with definite arteriovenous displacement In areas adjoining the discs there were several white exudates The inferior veins were dilated No hemorrhages were seen It was thought that these changes represented a diabetic retinitis and that the ocular pain might be related to the very poor vision The only previous examination of the eyes was on October 25 At that time no hemorrhages or exudates were seen On October 24 on intravenous pyelogram the renal and psoas soft tissue shadows were not remarkable After injection of the dye both kidneys were seen to function well The bladder was relatively large and there was a large filling defect at its base which represented prostate On October 28 x ray of the chest showed the heart great vessels and bony thorax were normal The lung fields were clear

DISCUSSION *For the first few days after operation* the patient made satisfactory progress The complication which led to his death appears to have been associated with the latter portion of the post operative period Several interesting developments took place during this portion of his illness Eleven days before death it was noted that the surgical incision was healing poorly and that infection had developed The urine became so foul smelling that fecal contamination through a fistula was suspected In the period after operation coinciding with the development of the infection the insulin dosage

necessary to maintain reasonable control of the diabetes increased from about 25 units to 55 units Even at this dosage the blood sugar remained well over 200 Between November 12 and November 17 there was a rapid decrease in the amount of insulin necessary and although he received no insulin on November 17 the blood sugar was 130 mg % and with no insulin on the following day it was 117 mg % After that no blood sugar determinations were made but the patient received no insulin and did not develop glycosuria Then on November 24 he suddenly became unconscious with evident central nervous system dysfunction There seems little doubt that during a resistant infection which had at first made it necessary to increase the insulin dosage there was secondarily a marked change in carbohy drate metabolism with amelioration of the diabetes To determine the cause of this one must review the conditions which simulate the effects of excess insulin administration or in which there is sudden decrease in availability of glucose (cf Table 29) First of all hepatic disease may lead to hypoglycemia as has been known since the classic experiments of Mann and Bollman on extirpation of the liver in the experimental animal The conversion of glycogen to glucose takes place mainly in this organ However liver function must be seriously deranged before hypoglycemia occurs approximately 20 per cent of normally functioning hepatic tissue is sufficient to prevent hypoglycemia in the resting state There was no clinical indication that this patient had any extensive damage to his liver Hypoglycemia may also be produced by a functioning tumor of the islet cells of the pancreas Certainly there was no indication in the preoperative period that this man had had any such disturbance In fact the reverse was true as he had had the classic clinical picture of diabetes mellitus for 10 years It would seem therefore that this diagnosis also can be readily excluded The activity of hexokinase is apparently responsible for the conversion of glucose to glucose 6-phosphate This reaction is subject to the influence of several hormones Insulin is necessary for the reaction but the reaction is apparently controlled by an in hibitor in the anterior pituitary Lack of anterior pituitary inhibitor and likewise lack of certain adrenal cortical substances will enhance the rate of the reaction and produce the effects of excess insulin administration These effects have been studied extensively in the ex perimental animal It was shown by Houssay in 1924 that removal of the pituitary gland from the dog increases the animal s sensitivity to insulin In 1930 he found that when toads and dogs in which diabetes had been produced by pancreatectomy were subjected to hy

Table 29 Causes of Hypoglycemia (modified after Conn and Loeb)

- I Functional hypoglycemia
  - A Increased islet cell function
  - B Anterior pituitary or adrenocortical hypofunction
  - C During pregnancy and lactation
  - D Idiopathic
  - E After drinking denatured alcohol (Smoke)
- II Secondary to hepatic disease
  - A Diffuse hepato-cellular involvement
    - 1 Carcinoma
      - a Secondary
      - b Primary
    - 2 Congestive heart failure
    - 3 Acute hepatitis
    - 4 Glycogen disease
    - 5 Diffuse cholangitis
    - 6 Cirrhosis of the liver
      - a Laennec s
      - b Biliary
    - 7 Toxic hepatitis due to chemical agents
    - 8 Fatty infiltration
- III Secondary to hypophysial deficiency (anterior lobe)
  - A Due to chromophobe adenoma
  - B Compression or invasion by tumors cysts inflammatory lesions granulomatous disease
  - C Infection abscess formation
  - D Atrophy
- IV Secondary to adrenocortical insufficiency
  - A Tuberculosis
  - B Atrophy of undetermined cause
  - C Bilateral hemorrhage in disease associated with hemorrhagic phenomena
  - D Neoplastic invasion
  - E Amyloid disease
- V Hypothyroidism
- VI Secondary to disease of the nervous system hypothalamic invasion or destruction

pophysectomy the severity of the diabetes was greatly diminished In 1936, Long and Lukens demonstrated that diabetes produced by pancreatectomy in the cat could be attenuated by removal of the adrenal cortex

Thyroidectomy will reduce the degree of glucose and nitrogen excretion in the depancreatized animal but does not influence survival to the same extent as removal of the anterior pituitary or the adrenal cortex Removal of the gonads the posterior pituitary or the adrenal medulla has no effect on the diabetes The present patient

exhibited no evidence of acute adrenocortical insufficiency This rare condition is almost invariably accompanied by rapid development of severe peripheral circulatory collapse which certainly was not present during the last few days of life It is well known that in human subjects under appropriate circumstances there may be sudden development of acute anterior pituitary insufficiency In 1914 Simmons described an autopsy on a woman with a history of puerperal sepsis who developed cachexia and gonadal deficiency A fibrosed pituitary body was found which he attributed to a septic embolism which had occurred in the postpuerperal period Sheehan described fresh infarcts in the anterior pituitary of women dying from collapse and hemorrhage at childbirth He suggested postpartum necrosis as a name for these lesions A patient presented at one of our conferences in 1946 had a chronic stenosing regional ileitis complicated by hypoglycemia She was found to have focal necrosis of the pituitary gland Certainly the sudden amelioration of the diabetes in the present case might be due to acute infarction of the anterior pituitary perhaps as a result of vascular thrombosis This might furnish an explanation for the pain over the eyes and in the back of the head which were described in the ophthalmological note The definite retinal arteriosclerosis suggests that the thrombosis may have occurred in a sclerotic vessel In view of the severe postoperative infection there is also the possibility of a septic embolus as postulated by Simmons The rapid development of a comatose state with evidences of hemiplegia flaccidity of the muscles and stiffness of the neck suggests that this patient may also have had a cerebral hemorrhage However these manifestations are completely compatible with the nervous system dysfunction that may result from severe hypoglycemia

Anatomical Diagnosis (Autopsy No 24014) History of diabetes mellitus with terminal hypoglycemia Hyaline islands of Langerhans and atrophy of pancreas Arteriosclerosis especially of coronary arteries Hypertrophy of bladder chronic cystitis subacute abscess at operative site Focal scars and chronic inflammation kidneys Abscess with necrosis of anterior lobe of hypophysis Purulent meningitis and ependymitis emphysema Glycogen in liver cell nuclei

The amelioration of the diabetes mellitus and the terminal hypoglycemia (blood sugar on the day of death was 32 mg %—information not available to the discusser prior to the conference) were explained by the complete necrosis of the anterior lobe of the hypophysis There were large abscesses in this area from which staphylococci and streptococci were cultured There was no evidence of a septic infarct and no evidence of extension of infection from a neighboring area It seemed likely that the lesion was the result of a blood borne infection from the operative site

SUMMARY This 68 year old white male who had had diabetes mellitus for ten years entered the hospital for a prostatectomy In the postoperative period he developed a wound infection which did not respond to antibiotic therapy and led to an increased need for insulin Suddenly there was amelioration of the diabetes but the patient became comatose Signs of severe central nervous system dysfunction appeared and he died It was postulated that the terminal episode was due to hypoglycemia and that the change in carbohydrate metabolism was secondary to infarction of the anterior lobe of the pituitary gland NECROSIS OF THE ANTERIOR HYPOPHYSIS DUE TO MULTIPLE ABSCESSES was found at autopsy

XXIV

(#441345 Admitted November 2 1947
Died November 22 1947)

THIS 46 year old white woman complained of loss of weight anemia abdominal discomfort and generalized fatigue of four months duration She had a tonsillectomy 6 years prior to admission following repeated sore throats There was complete edentia for 8 years

Six years before admission she developed pain localized to the knee joints ankles shoulders elbows wrists and fingers and accompanied by swelling and redness of the joints She was afebrile Three years later she received two injections of a gold salt In September 1946 she went to Florida where she remained until May 1947 During this time the pains disappeared and she was free of symptoms except for some contracture at both elbows and limitation of movement of the fingers In May 1947 she developed anorexia and generalized fatigue She lost weight rapidly and in July 1947 began to have daily elevation in temperature which sometimes rose to 104 or 105 in the afternoon On several occasions she had chilly sensations lasting 10 or 15 minutes In August 1947 she was found to have anemia with leukopenia She had intermittent episodes of epigastric discomfort but x ray examination revealed only a diverticulum of the duodenum

PHYSICAL EXAMINATION on admission T 100 4 P 110 R 20 B P 110/78

The patient was very emaciated and weak There was generalized lymph node enlargement the nodes feeling rubbery and discrete There were typical findings of rheumatoid arthritis in the hands with ulnar deviation of the fingers a sclerodermatous appearance of the skin and atrophy of the muscles There was also a generalized muscular atrophy The pupils reacted normally visual fields were intact ophthalmoscopic examination revealed no abnormalities There were ulcers on the soft palate The thyroid was normal The lung bases descended poorly and inconstant coarse rales were heard at the left base The heart was slightly enlarged to the left The aortic second sound was accentuated and there was a coarse systolic murmur heard at the base To the left of the sternum there was a pericardial friction rub A protodiastolic gallop was heard at the apex The liver was percussed 2 fingerbreadths below the costal margin in the mid clavicular line In the epigastrium there was tenderness on pressure and a mass which was thought to be the liver The spleen could not be palpated There was edema of the ankles The deep tendon reflexes were equal and active

COURSE IN THE HOSPITAL The temperature rose to 101 or 102 each day During the first week she received three transfusions and had a pyrexial reaction following each Her temperature was lower during the second week but later rose at times to 104° Rales appeared at the right lung base and she was placed on penicillin for three days Her temperature fell to normal for one day and penicillin was discontinued Because of the pericardial friction rub and enlargement of the heart a pericardial paracentesis was attempted but was not successful She showed no signs of pericardial tamponade and the venous pressure was only slightly elevated On November 13 she had a Jacksonian type of convulsion with deviation of the eyes to the left winking of the left lid and generalized facial twitching with clonic movements of the left arm and leg She had several such episodes without residual neurological changes until November 18 when she became comatose and developed a left hemiparesis There was bilateral papilledema and deviation of the eyes to the left She did not regain consciousness

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin 8 gm hematocrit 32 icterus index 6 sedimentation rate 35 mm per hour Leukocyte count was 3 700 with 18% myelocytes 6% juvenile neutrophils 19% segmented neutrophils 53% lymphocytes 4% monocytes Two nucleated red blood cells were seen per 100 white cells Platelet count 200 000 reticulocyte count 1 5% The urine showed a specific gravity of 1 020 and a trace of albumin No red cells white cells or casts were seen Blood nonprotein nitrogen 28 mg % later rose to 57 mg % serum albumin 2 3 gm % and serum globulin 4 5 gm % phosphorus 2 1 mg % calcium 9 7 mg % thymol turbidity test 28 units cephalin flocculation 4 plus

Phenolsulfonphthalein excretion in two hours was 45% Urea clearance was 43% and 48% of normal standard clearance The stool showed a positive guaiac test no ova or parasites were found

Agglutination tests for typhoid paratyphoid brucella and proteus were negative Numerous gastric washings and sputum examinations were negative for tubercle bacilli Tuberculin tests (1st and 2nd strength PPD) were negative

Lumbar puncture done on November 13 showed initial pressure 76 mm normal dynamics No cells were found Smear and culture were negative Protein was 50 mg % Electrocardiogram showed a rate of 115 waves of low amplitude T waves were flat Changes were compatible with the diagnosis of pericarditis

X rays of the chest on November 2 showed increase in cardiac diameter both to the right and to the left with aortic tortuosity and widening Congestive changes were prominent in both hilar areas extending out into both lung fields On November 3 routine films of the skull were normal Barium enema was negative Gastrointestinal series on November 6 showed no lesions

DISCUSSION In this case one is presented with a clinical picture having so many manifestations that it is difficult to find one disease

which will satisfactorily explain them all The crucial point is to decide whether the acute illness which began in late 1947 and continued to her death was a separate entity or whether it was only part of a single disease process which had its onset several years previously with the polyarthritis If we assume first that one disease will account for all of the features two possible diagnoses seem worthy of serious consideration

Systemic lupus erythematosus occurs frequently in white females in middle life This disease may begin with the classic picture of rheumatoid arthritis Remissions and exacerbations in the joint manifestations may occur over a period of several years before any other signs appear High spiking fever may occur and in some cases may be the first and the only manifestation of systemic lupus for many months Anorexia and abdominal pain are common manifestations and anemia and leukopenia with an abnormal myelocytic picture may also be observed The occurrence of serous membrane involvement is well known and the combination of polyarthritis pericarditis with effusion and pleurisy points strongly to systemic lupus In approximately half of the cases the illness runs its entire course without there being any cutaneous involvement In the present case the focal convulsions and hemiplegia which led to a clinical diagnosis of brain tumor might have been due to hemorrhage This type of cerebral dysfunction is seen in a significant number of patients with lupus erythematosus Renal involvement is of course common in this disease

The second disease to be considered is subacute bacterial endocarditis Suppose that in the summer of 1947 bacteria became implanted on a heart valve previously damaged by rheumatic disease or even by lupus erythematosus The anemia loss of weight fever the intracranial episode and the evidence of renal involvement would all then find a very reasonable explanation The absence of petechiae and of clubbing of the fingers and splenomegaly does not exclude this diagnosis The fever did seemingly subside on penicillin but was too irregular from then on to make this a telling observation Pericardial effusion may occur in the course of bacterial endocarditis and in the absence of cardiac failure is more frequent than a large unilateral pleural effusion No blood cultures were made

If one considers that the patient had rheumatoid arthritis which became complicated by a second disease then what diagnoses must be considered? The most likely possibilities would seem to be either an infection such as tuberculosis or brucellosis or one of the lymphoma group of diseases

Tuberculosis might well explain the involvement of the pericardium and the pleura If the tuberculosis were disseminated this degree of fever would not be unusual The anemia might be attributable to an associated nutritional deficiency resulting from a long standing febrile illness with anorexia and marked loss of weight One would have to account for the cerebral episode on the basis of a tuberculoma in the cortex of the right motor area, multiple lesions might explain the signs of increasing intracranial pressure with loss of consciousness Numerous gastric washings were done but no tubercle bacilli could be found and tests with first and second strength purified protein derivative were negative

There is no real basis for further consideration of the possibility of chronic brucellosis It is conceivable that some type of lymphoma invaded the pleura pericardium and intracranial structures There was slight generalized lymph node enlargement but the spleen was not enlarged The evidence in favor of lymphoma is so meager that this possibility may be dismissed

I cannot escape the impression that the final intracranial episode was on a vascular basis If one then looks at the entire sequence of events including the synovial manifestations one has a picture which can be most satisfactorily accounted for by a diagnosis of systemic lupus erythematosus

Anatomical Diagnosis (Autopsy No 20921) History of rheuma toid arthritis Disseminated lupus erythematosus Necrosis of collagen with overlying fibrinous thrombus at base of mitral valve Foci of collagen degeneration with associated inflammatory cells in myocardium and about esophagus Periarterial fibrosis in spleen Hyaline masses in renal glomeruli Organized and fresh pleuritis and pericarditis Anaphylactoid pneumonitis Fibrinoid degeneration of walls of arteries in stomach and bladder with aneurysm formation Intracerebral and subdural hemorrhage left occipital lobe History of anemia Central atrophy and congestion in liver Fat in periportal liver cells Duodenal diverticulum

The epicardial surface was thickened by gray fibrous tissue and super ficial fibrin deposit There was a small nodular thickening of the free margin of the mitral valve The pleural surfaces were everywhere thickened with fibrous adhesions over which many fibrinous deposits were found The bladder was contracted and its mucosa raised by edematous hemorrhagic folds several of which appeared to be superficially ulcerated There was a pressure cone at the base of the cerebellum In the right occipital lobe there was a large ragged hole in the brain filled with blood clot and the surrounding brain tissue was infiltrated with hemorrhage

Microscopically lesions were found which were typical of systemic lupus erythematosus There were foci of collagen degeneration with associated inflammatory cells in the myocardium and in the connective tissue about

the esophagus as well The spleen showed the periarterial fibrosis characteristic of lupus and there were necrotic hyaline loops in the glomeruli of the kidneys *There were organized and fresh pericarditis and pleuritis* The lungs showed lesions suggestive of anaphylactoid pneumonitis In the stomach and in the bladder there were arteries with completely necrotic walls which appeared smudgy or fibrinoid Several of these affected arteries in the stomach showed walls which had given way with the formation of aneurysms Aneurysmal formation in the arterial lesions of lupus is uncommon It was possible that the hemorrhage in the brain resulted from the rupture of a small aneurysm similar to those in the stomach

SUMMARY This 46 year old white woman had arthritis of the rheumatoid type six years before death Five months before demise she developed fever loss of weight fatigue and abdominal discomfort and was found to have anemia and leukopenia Examination showed fever loss of weight asthenia generalized lymph node enlargement rheumatoid deformities in the hands with periarticular muscular atrophy and scleroderma like changes in the skin soft palate ulcerations cardiomegaly with a systolic murmur pericardial friction rub and protodiastolic gallop rhythm hepatomegaly and peripheral edema She continued to run fever and had *Jacksonian convulsions* She became comatose and developed a left hemiparesis Laboratory studies showed anemia leukopenia with 18 per cent myelocytes and nucleated red cells in the smear hyperglobulinemia and later azotemia Tuberculosis subacute bacterial endocarditis and systemic lupus erythematosus were discussed as possible explanations for this illness A diagnosis of SYSTEMIC LUPUS ERYTHEMATOSUS seemed to afford the most satisfactory explanation of the entire illness At autopsy this proved to be the correct diagnosis

Tuberculosis might well explain the involvement of the pericardium and the pleura If the tuberculosis were disseminated this degree of fever would not be unusual The anemia might be attributable to an associated nutritional deficiency resulting from a long standing febrile illness with anorexia and marked loss of weight One would have to account for the cerebral episode on the basis of a tuberculoma in the cortex of the right motor area multiple lesions might explain the signs of increasing intracranial pressure with loss of consciousness Numerous gastric washings were done but no tubercle bacilli could be found and tests with first and second strength purified protein derivative were negative

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nauseated vomited frequently was restless was often disoriented at night and became drowsier as her uremia increased During the last 10 days she was treated with streptomycin and penicillin which had no apparent effect During the third week a blotchy eruption appeared over the face This had a butterfly distribution across the malar eminences and the bridge of her nose The lesions consisted of small areas of ecchymosis under the skin She developed a conjunctivitis with several subconjunctival hemorrhages During the last two weeks this eruption gradually subsided

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin was 11 gm sedimentation rate 40 mm per hour hematocrit 38 Leukocyte count was 10 200 with 1% myelocytes 3% juvenile neutrophils 74% segmented neutrophils 1% eosinophils 18% lymphocytes and 3% monocytes Examination of the smear showed no abnormalities Platelets were adequate in number Blood calcium was 8 8 mg % phosphorus 7 mg % chlorides 105 mEq CO_2 combining capacity 24 mEq *total serum protein 5 4 gm % with 2 6 gm % of globulin cholesterol 158* mg % The nonprotein nitrogen on admission was 62 mg % on March 28 87 mg % and on April 21 160 mg %

Stool guaiac positive on admission subsequently was guaiac negative Specific gravity of the urine fluctuated between 1 008 and 1 018 with large amounts of albumin Sediment showed innumerable white blood cells many red blood cells and numerous granular and hyaline casts Urine culture showed *Escherichia coli* Blood cultures taken on several occasions showed no growth at the end of 7 days

Tests of renal function showed 16 per cent excretion of phenolsulfonphthalein in 2 hours Urea clearance was 6% of normal in the first specimen and 7% in the second

Tuberculin tests were negative X ray of the chest showed an enlarged heart with prominence in the pulmonic area The esophagus was not displaced by the left auricle

DISCUSSION The central feature of this disease picture was the apparent diffuse renal involvement with rapidly progressive symptomatic uremia The urine contained a large amount of albumin and numerous cellular elements The diagnostic possibilities to be considered are

(1) Arteriolosclerotic renal disease
(2) Amyloidosis
(3) Glomerulonephritis
(4) Collagen vascular disease (systemic lupus erythematosus)
(5) (Embolic) Nephritis associated with bacterial endocarditis

There is little to suggest that this patient had arteriolosclerotic nephritis There was no hypertension during her hospital stay and the eye grounds did not indicate that her pre admission episodes were due to hypertensive encephalopathy The temporary rise in systolic blood pressure seems most likely to have been a secondary

manifestation associated with the agitated state and convulsive e sodes There seems to be no indication that these were episodes paroxysmal hypertension such as one sees with pheochromocytor

There is nothing here to suggest primary amyloidosis The li and spleen were not enlarged This rare syndrome is difficult to e clude with finality but I have never known it to develop in such setting with such a rapidly progressive illness as this patient had

The next possibility is glomerulonephritis On first consideratio this seems to be an outstanding probability but there are certain fe tures which make it unlikely Persistent fever without obvious loc infection would be unusual In the terminal weeks absence of hype tension the relatively high specific gravity of the urine in the presenc of uremia the marked albuminuria and hematuria are somewha against this diagnosis Moreover the joint pains and valvular lesio would have to be explained on some other basis Glomerulonephriti and rheumatic fever are not commonly encountered in the same patient

The peculiar features of this case suggest that the patient had either lupus erythematosus or subacute bacterial endocarditis It may be difficult to distinguish between the two

It is relatively easy to recognize systemic lupus erythematosus when the patient shows all of the characteristic manifestations including fever arthritis cutaneous lesions sterile effusion in serous cavities and a picture of chronic nephritis However the course of the disease is characterized by fluctuations in the degree of activity which may be great at times followed by periods of relative freedom from symp toms In the recrudescences the active lesions may be confined to relatively restricted areas In one attack the only manifestations may be fever and a pleural effusion whereas in another the important abnormality may be a pericardial effusion and in still another the cutaneous manifestations may be quite prominent In this way the disease picture only unfolds over a period of years, and the patients may be seen in several exacerbations before enough perspective can be gained to make the diagnosis obvious Fever is almost universally present as is arthritis at some stage The location of the cutaneous lesions in this case was very suggestive but the appearance of the lesions was not diagnostic Rarely does the endocarditis of lupus present such striking clinical evidence of valvular disease particularly of the aortic valve The renal manifestations in this case are quite compatible with this diagnosis but rarely is the serum globulin below 3 gm % in patients with active disease Lesions of the cerebral vessels

are quite common and convulsions not infrequent In this case both the tendency to leukopenia and the progressive anemia are compatible with lupus but the anemia may have been secondary to the progressive azotemia

Four features in combination are necessary to make an unequivocal diagnosis of subacute bacterial endocarditis (1) valvular defect or congenital lesion (2) febrile course (3) embolic phenomenon (4) positive blood cultures Renal involvement leading to uremia is not uncommon and there is usually no associated rise in blood pressure The sterility of the blood cultures does not rule out the possibility of bacterial endocarditis in this case for two reasons (1) The cultures were not retained and examined for a long enough period Not infrequently organisms will not grow out in detectable numbers for two or three weeks, and in this case the cultures were reported negative after only seven days (2) This patient received penicillin When this happens the blood may be sterilized and the diagnosis is made very difficult There is evidence that nephritis may be more common in patients in a bacteria free stage of this disease Petechiae are less frequent but it is conceivable that the conjunctival lesions and the purpuric facial lesions were of embolic origin The amount of penicillin given this patient in the terminal phase of the illness was insufficient to constitute a therapeutic test of any diagnostic value The almost certain presence of rheumatic heart disease is the most telling finding in the differential diagnosis This leads me to conclude that the patient had rheumatic endocarditis and glomerulonephritis

ANATOMICAL DIAGNOSIS (Autopsy No 21764) Subacute glomerulonephritis Pulmonary subcutaneous and generalized tissue edema History of uremia coma and butterfly rash Splenomegaly with periarterial fibrosis Scarring of mitral and aortic valves Round cell foci in epicardium and striated muscle Lupus erythematosus disseminatus(?) Chronic pyelitis and cystitis Myomata uteri

The right ventricle was thicker than normal and the left ventricle was also slightly hypertrophied The left auricle had a distinctly thickened wall There was a thick fibrous ridge on the line of closure of the anterior mitral leaflet One or two of the chordae tendineae were thickened The aortic valve was scarred and there was fibrous thickening of each leaflet Both valves were judged to be incompetent The spleen was definitely enlarged The kidneys were larger than normal and had thin capsules which stripped easily The cut surface showed a pale wide cortex in which the striations were difficult to make out

Microscopically there was a most extreme glomerulonephritis with virtually every nephron involved The glomerular lesions were fairly acute with intercapillary cells scarring and epithelial crescents blocking Bow

man s capsular spaces The tubular epithelium was filled with colloid droplets The lesion suggestive of lupus erythematosus was in the spleen where there were numerous areas of periarterial fibrosis The valvular thickening in the heart as well as the minimal perivascular scarring might well be related to childhood rheumatic disease

SUMMARY This 28 year old Negro female had a history of rheumatic fever in childhood Eight years before death she had a depression requiring hospitalization Three years before entry there was bilateral lower abdominal pain anemia and leukopenia The terminal illness was characterized by fever productive cough chest pain facial edema headache vomiting and convulsions with hypertension Examination revealed fever coma cardiomegaly systolic and diastolic murmurs peripheral signs of aortic insufficiency and edema She was uremic and developed anemia and a purpuric eruption of butterfly distribution on the face There was albuminuria pyuria hematuria and cylindruria with markedly reduced phenol sulfonphthalein excretion The central feature of the picture was the renal insufficiency with the changes characteristic of diffuse kidney involvement The strong clinical evidence of aortic insufficiency led to a diagnosis of rheumatic fever and glomerulonephritis Lesions suggestive of SYSTEMIC LUPUS ERYTHEMATOSUS were found at autopsy although the kidney showed typical GLOMERULONEPHRITIS, and there was CHRONIC RHEUMATIC VALVULITIS

XXVI

(#363666 1st Admitted September 24 1945 to October 2 1945
Re admitted October 18 1945 Died November 1 1945)

THIS 48 year old Jewish painter on his first admission complained of diarrhea and abdominal cramps of 2 years duration and of progressive loss of vision worse during the previous 6 months

Two years before while working as a painter he was seized with abdominal cramps and diarrhea After that he had frequent attacks of diarrhea lasting from 2 to 7 days during which time he would have 10 to 12 loose stools a day There was mild crampy pain mainly in the lower left quadrant aggravated by drinking or eating He received a variety of medications with no improvement Frequently he was nauseated and had periods of vomiting During the year before admission he had shortness of breath and swelling of the ankles He complained at times of a burning sensation beneath the sternum For a year he had had urticarial lesions following ingestion of certain foods For six months he had noted that the vision in the right eye had failed considerably During the two years he had lost 23 pounds in weight He drank a quart of whiskey and 12 bottles of beer every weekend

PHYSICAL EXAMINATION on first admission T 98 6 P 66 R 24 B P 142/80

The patient showed signs of weight loss The fingers and toes were markedly clubbed A cataract was noted in the right eye The fundi could not be clearly visualized The pupils reacted normally All teeth were missing The tonsils were small There was no lymph node enlargement The thyroid was normal A few wheezes were heard at the end of inspiration over the left chest The heart was not enlarged The apical impulse was not visible or palpable The heart sounds were clear no murmurs were heard the rhythm was regular The peripheral vessels were sclerotic The abdomen was flat No organs or masses were made out There were internal hemorrhoids The prostate was not enlarged The reflexes were equal and active

LABORATORY DATA The serologic test for syphilis was negative The hemogram showed red blood cells 4 million hemoglobin 10 5 gm hematocrit 32 icterus index normal *sedimentation rate 25 mm per hour* Smear showed numerous microcytic and hypochromic cells Total leukocyte count was 4 960 with 10% juvenile neutrophils 50% segmented neutrophils 2% eosinophils 36% lymphocytes and 2% monocytes Stools were soft brown and contained no blood or parasites Bacteriological examina

tion of the stools revealed no pathogenic organisms Urine was normal except for an occasional white blood cell in the sediment X rays of the gastrointestinal tract on September 29 were normal except that at the end of 5 hours the terminal ileum appeared to be deformed and somewhat constricted suggesting the presence of an inflammatory process Barium enema showed a normal large intestine

COURSE IN THE HOSPITAL The patient seemed to improve as far as his diarrhea and abdominal cramps were concerned He was very nervous and had three to four stools a day He was discharged on October 2 Final diagnosis on that admission was arteriosclerosis chronic alcoholism and diarrhea of unknown cause

SUBSEQUENT COURSE The patient was admitted again on October 18 at which time he stated that 6 days previously he had awakened with a sharp pain in the back between the shoulder blades The pain was constant dull and persisted for 3 days The day of admission he had nausea and vomiting

PHYSICAL EXAMINATION on second admission T 102 P 80 R 20 B P 118/86

The patient was breathing normally Ecchymoses were noted over both ankles and there was angioneurotic edema of the right hand and forearm The lungs were clear to percussion and auscultation The heart sounds were faint The pulses were equal and regular but weak There was generalized abdominal soreness Otherwise the physical examination was the same as on the previous admission

LABORATORY DATA Blood calcium was 9 3 mg % phosphorus 4 5 mg % phosphatase activity 3 1 units Refractive index showed 7 2 gm of protein in the serum Uric acid was 5 3 mg % Barium enema on October 23 demonstrated no organic lesion In the gastrointestinal series at five hours there was some retention in the stomach and the barium was distributed through the entire small intestine showing evidence of segmentation X ray of the chest revealed normal heart and aorta The lungs were clear The lower spine appeared normal in the x ray X ray of the left hip revealed hypertrophic arthritis with sclerosis of the inferior border of the acetabulum and some early cystic change about it A second gastrointestinal series done on October 25 demonstrated some deformity of the small bowel thought to indicate a low grade inflammatory lesion The tuberculin test (2nd strength PPD) was positive Hemogram showed red blood cells 5 4 million hemoglobin 12 8 gm hematocrit 42 icterus index 3 sedimentation rate 8 mm per hour Total leukocyte count was 8 300 with 1% myelocytes 9% juvenile neutrophils 54% segmented neutrophils 2% eosinophils 5% monocytes and 39% lymphocytes Stool examinations showed no blood and no parasites were found One urine examination showed 1–2 red blood cells and 3–5 white blood cells per high power field as well as a trace of albumin An electrocardiogram taken on October 19 was normal Sigmoidoscopy on October 24 showed no lesions

COURSE IN THE HOSPITAL The patient often complained of crampy abdominal pains readily relieved by atropine It was the opinion that he had regional ileitis At 10 A M on November 1 he complained to the nurse

that he was having one of his nervous attacks He was gasping for breath holding his hands over his abdomen The pulse could not be obtained He rapidly became cyanotic the blood pressure became unobtainable and he died There was no complaint of pain

DISCUSSION A striking feature of this case is the contrast between the numerous complaints over the two year period and the sparsity of objective findings during the two hospital admissions Let us list the complaints and signs noted so that we might pick some substantial finding about which the analysis of the case can be built attacks of crampy abdominal pain with diarrhea 20 pound weight loss attack of pain between scapulas swelling of right forearm wrist hand and right ankle urticarial eruptions episodes of shortness of breath and burning beneath the upper sternum low grade fever clubbed fingers and toes ecchymotic lesions over the ankles and finally anxiety attacks one of which preceded his sudden collapse and unexpected death

First let us examine the possible causes of acquired symmetrical clubbing of the fingers and toes as listed in Table 30 By far the majority of cases are associated with some chronic disease of the respiratory tract for which there was no evidence in this case—certainly not for one which could explain the chronic diarrhea

Cyanotic congenital heart disease is commonly associated with clubbing but this obviously was not present in this man In spite of the normal chest x ray he could conceivably have had a thoracic or upper abdominal aneurysm which could be associated with clubbing but such a lesion would not be expected to produce several varieties of pain diarrhea and sudden death without having made itself more evident The blood serologic test for syphilis was negative There was nothing to suggest bacterial endocarditis

Clubbing may be associated with certain forms of hepatic cirrhosis but the course of this illness could not be explained by such a diagnosis He had been a fairly heavy drinker but if cirrhosis was present it would in my estimation be an incidental finding

It is well known that certain chronic disorders of the gastrointestinal tract particularly those associated with diarrhea may be accompanied by clubbing Ulcerative colitis could not have been present in this case as judged by the normal sigmoidoscopic examination normal barium enema and absence of blood in the feces Intestinal tuberculosis might have caused the lesion in the terminal ileum and the tuberculin test was positive However although there was the picture of recurrent attacks of upper abdominal pain with

Table 30 Causes of Clubbing of the Fingers and Toes

I Chronic pulmonary disease
- A Acquired
  1 Abscess
  2 Tuberculosis
  3 Bronchiectasis
  4 Emphysema
  5 Carcinoma of the lung
  6 Other intrathoracic neoplasms
  7 Chronic asthma and emphysema
  8 Pneumonoconiosis
  9 Actinomycosis
- B Congenital
  1 Cystic disease
  2 Bronchiectasis

II Circulatory disease
- A Acquired
  1 Subacute bacterial endocarditis
  2 Aortic aneurysm
  3 Mitral stenosis and regurgitation
- B Congenital
  1 Cyanotic type with venous arterial shunt
  2 Pulmonary hemangioma

III Disease of the gastrointestinal tract and biliary tree
- A Acquired
  1 Cirrhosis of the liver
    a Biliary
    b Cholangiolitic
    c Laennec s
  2 Ulcerative colitis
  3 Intestinal tuberculosis
  4 Regional enteritis
  5 Chronic dysentery
    a Bacillary
    b Amebic
- B Congenital
  1 Multiple polyposis of the colon

IV Miscellaneous
- A Congenital familial or hereditary clubbing
- B Unilateral clubbing
  1 Arteriovenous aneurysm
  2 Pancoast or superior sulcus tumor
  3 Subclavian or innominate aneurysm
- C Post thyroidectomy (acropachy)

diarrhea there was no evidence of pulmonary tuberculosis and one would have to invoke another explanation for the other findings and the sudden death The normal barium enema and lack of bleeding seem to rule out multiple polyposis There may have been a chronic

pancreatitis to explain the weight loss the upper abdominal pain and the recurrent attacks of diarrhea but the attacks of dyspnea the burning substernal pain and other changes indicate that such a lesion alone could not explain the picture

I know of only one other explanation for such a marked degree of clubbing and that is the familial type We do not know how long this clubbing had existed There was no record as to its time of onset or any indication of progression over the two years of his illness I would be inclined to believe that it was the familial type and probably unrelated to his present illness That leaves us with the probable explanation of his clubbing but not of the illness which led to death However in considering these various causes of clubbing we have seen that this patient had a very bizarre illness with a variety of manifestations which are difficult to explain under a single diagnosis

Now we have one further feature to explore and that is the sudden death It has been pointed out that the majority of sudden deaths are due to some cardiovascular episode Those which lead to almost instant death as occurred here are (1) massive pulmonary embolism (2) coronary thrombosis with ventricular fibrillation and (3) hemorrhage Now the sudden exitus without any complaint of pain suggests arterial hemorrhage which may produce sudden death from (a) loss of blood or (b) compression of some vital structure as in bleeding into the pericardium

We have already suggested that this man did not have a syphilitic aneurysm from which he might have bled Moreover there was no evidence of disease of the heart which might have led to sudden death Some type of generalized disease of the smaller vessels such as *periarteritis nodosa* might have been present This would explain all of the findings Low grade fever and weight loss are common attacks of abdominal pain with diarrhea may occur when the vessels of the gut wall or the nerves supplying the intestine are affected Attacks of dyspnea angioneurotic edema and urticaria are not infrequent Central nervous system lesions may produce a picture of anxiety and nervousness and finally the sudden death may have resulted from hemorrhage from a mesenteric vessel or from a coronary vessel leading to tamponade of the heart or coronary thrombosis or embolism

ANATOMICAL DIAGNOSIS (Autopsy No 19663) Generalized coronary and aortic arteriosclerosis with complete occlusion of the anterior descending and right coronary arteries and extreme narrowing and probable

occlusion of the left circumflex artery Scarring of myocardium Fresh myocardial infarct of left ventricle Periarteritis nodosa in heart adrenals intestines and mesentery Ulceration and perforation of sigmoid colon with localized peritonitis Chronic bronchitis with eosinophilic infiltration Chronic pyelonephritis Pyelitis cystica Pulmonary emphysema Chronic atrophic gastritis Calcified tubercle in right lower lobe Tubercles in peri bronchial lymph node

There were hemorrhages beneath the endocardium of the right ventricle and on section also in the heart muscle The endocardium of the left ventricle appeared thickened The posterior ventricular wall was thinner than the anterior wall and on section the normal myocardium was replaced by whitish areas and small red dots Beneath the epicardium over this area there were hemorrhagic patches The left anterior descend ing artery was sclerotic its lumen being practically occluded as was that of the circumflex branch The colon was small and contracted and in one place there was a discolored area 3 cm in diameter in the center of which there appeared to be a mucosal hemorrhage

Histologically the anterior descending coronary artery showed marked arteriosclerotic changes as did the left circumflex In addition there was infiltration of the walls of the coronary arteries with inflammatory cells The lumen of the left circumflex was almost completely obliterated There was an old infarct of the myocardium with necrosis and hyalinization of muscle and many necrotic nuclei There was a fresh infarct in the myo cardium of the left auricle with considerable hemorrhage visible There was also a fresh infarct in the left ventricle with necrosis and some leuko cytic infiltration Many of the small coronaries seen were thrombosed and showed intimal proliferation Others had many lymphocytes and eosino phils within their walls strongly suggesting periarteritis nodosa The lungs contained numerous accumulations of lymphocytes and eosinophils about and within the walls of the alveoli Many small arteries contained thrombi others showed marked intimal thickening and degeneration of the media along with the presence of mononuclear cells and eosinophils Throughout the intestines numerous periarteritic lesions were seen in all stages from acute necrosis of the media and the presence of eosinophils to the healed stage with fibrosis of the destroyed portion of the artery intimal proliferation and recanalization of some of the thrombi In the sigmoid colon there was an ulcer extending through the wall of the intestine and producing a localized peritonitis In the mesentery were two throm bosed vessels whose intima was greatly thickened Blood vessels about the adrenals showed periarteritic lesions In the kidneys there were occasional hyalinized glomeruli and numerous areas of round cell infiltration repre senting foci of chronic pyelonephritis The renal vessels showed moderate arteriosclerotic change

SUMMARY This 48 year old Jewish painter had recurrent attacks of cramps and diarrhea for 2 years attacks of dyspnea edema and urticaria for one year loss of weight and failure of vision in one eye Examination revealed loss of weight and clubbing of fingers and toes He was nervous and apprehensive X rays showed evidence of an inflammatory lesion in

the ileum Three weeks before death he had pain between the scapulas followed by nausea and vomiting Ecchymoses were noted over the ankles There was angioneurotic edema of the right hand The heart sounds were distant Abdominal palpation revealed generalized soreness Films of the small intestine indicated an inflammatory lesion He had a sudden attack of respiratory difficulty cyanosis and hypotension and died The protean nature of this patient s complaints with little in the way of objective findings was noteworthy The causes of clubbing of the fingers were discussed and it was thought that this condition was familial The bizarre manifestations together with the sudden death suggested some type of arterial disease *and a diagnosis of periarteritis nodosa was made Autopsy revealed* coronary arteriosclerosis and lesions of periarteritis nodosa with occlusion of the anterior descending artery and a fresh MYOCARDIAL INFARCT involving the left ventricle PERIARTERITIS NODOSA was also present in other tissues

XXVII

(#390690 Admitted September 9, 1947 Died October 17, 1947)

THIS 21 year old Negro female complained of cough of 4 months duration She had had pneumonia in 1942 1944 and again in 1945 In July 1946 she was admitted because of abdominal cramps nausea and vomiting A mass palpable in the right lower quadrant was thought to be a tubo ovarian or an appendiceal abscess Hemoglobin was 7 5 grams and the leukocyte count 24 000 Because of anemia an overactive heart with a systolic murmur tibial ulcers of 2 years duration and long slender extremities which were out of proportion to the length of her trunk the patient was thought to have sickle cell anemia On occasions preparations showed as much as 80 per cent sickling

After discharge she got along fairly well until May 1947, when she had a chest x ray and was advised to report for examination She had had a h ad cold and a cough productive of foul sputum greenish in color and occasionally blood stained For several weeks there had been malaise anorexia chilly sensations and night sweats Examination revealed rales at the left lung base and an increase in the leukocyte count In July 1947 further x ray studies revealed an infiltrative lesion in the 2nd left interspace with questionable cavity formation The leukocyte count was 16 800 with 16 per cent eosinophils Sputum culture showed *Escherichia coli* proteus Neisseria and pneumococci No tubercle bacilli could be found The stools were negative for parasites X rays later in July showed some resolution of the pulmonary process In August 1947 bronchoscopic examination revealed a purulent discharge from the left lower lobe Bronchograms demonstrated ectasia involving the bronchi to the left lower lobe and lingula There was no reaction following the introduction of Lipiodol She was admitted a few days later for treatment

PHYSICAL EXAMINATION on admission T 100 P 82 R 20 BP 115/65

The patient was a poorly nourished mentally retarded young Negro female She coughed frequently producing foul greenish sputum The extremities were long and fingers were spider like There was fusiform enlargement of the phalangeal joints The mucous membranes were pale but there was no icterus There was no generalized lymphadenopathy The thyroid isthmus was enlarged The tonsils were moderate in size The pharynx was not injected The pupils were normal The retinal veins were tortuous The breasts were normal There was a lag and diminished expansion of the left chest There was dullness to percussion over the entire left

thorax with moist and crackling rales on inspiration There was no venous distention The heart was enlarged to the left The sounds were not remarkable P_2 was accentuated There was a rough systolic murmur in the pulmonic area and a palpable thrill was transmitted to the carotid arteries The liver was felt 3 fingerbreadths below the costal margin The spleen was palpable There was tenderness in both lower quadrants with moderate rigidity in the right lower quadrant Pelvic examination revealed a walnut sized tender mass posterior to the right fornix with induration about it

COURSE IN THE HOSPITAL Treatment with penicillin and a sulfonamide was begun The cough and volume of sputum diminished and the sputum became less foul Her appetitie improved but during the first week she had intermittent pain in the right lower quadrant The x rays revealed a questionable cavity in the left lung at the level of the 2nd left interspace but sputum and gastric washings as well as material aspirated bronchoscopically revealed no tubercle bacilli On October 1 bronchoscopic examination was repeated and a bronchogram made Following bronchoscopy the patient had urinary retention and was catheterized The temperature began to rise on October 4 subsequently reaching a level of 103 to 104 and on October 9 105 On October 5 she complained of malaise anorexia and frontal headache and had a stiff neck The findings in the chest were unchanged There was no increase in cough or amount of sputum The leukocyte count was not elevated The spinal fluid contained only 3 mononuclear cells Cultures were negative On October 9 she complained of constant sharp pain in the right subcostal region and less marked pain under the midsternal area Both were increased with deep inspiration She began to vomit at frequent intervals She looked acutely ill and the leukocyte count rose to 14 000 The urine contained 3 plus albumin with 10 white blood cells numerous red blood cells and a few granular casts per high power field Penicillin and the sulfonamide were discontinued On October 9 *Escherichia coli* were grown from the urine and the patient was placed on streptomycin Lumbar puncture on October 14 revealed 20 mononuclear cells per cu mm She continued to have high fever with tachycardia On October 16 the temperature reached 107 and the leukocyte count had risen to 20 000 Lumbar puncture showed normal spinal fluid except for 40 mononuclear cells per cu mm The patient became disoriented and confused at times being almost maniacal There were involuntary movements of the head body and arms but she had no convulsions A Babinski reflex was present on the left side She became more delirious and the following day she was comatose and died

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin was 12 gm hematocrit 39 icterus index 5 sedimentation rate (corrected) 12 mm per hour The leukocyte count was 17 700 with 5% eosinophils No sickling of the red blood cells was seen in many preparations Several blood cultures were sterile

DISCUSSION In summing up the problem before us we have a young Negro woman who had many of the constitutional defects seen in sickle cell disease There can be little doubt that she had a chronic

pulmonary infection associated with bronchiectasis, as well as some type of inflammatory disease in the pelvic region Finally there was the terminal phase of her illness following the instillation of Lipiodol which was associated with high fever and leukocytosis and pleocytosis in the cerebrospinal fluid Can this entire picture be explained on the basis of the one specific disease or was some other factor responsible for the terminal illness which developed rapidly and was associated with such a marked febrile reaction and a dramatic change in the clinical picture?

The evidence certainly seems to support the belief that this patient had a suppurative process in the left lower lobe with bronchiectasis This may well have had its beginning with pneumonitis and atelectasis The attacks of so called pneumonitis may have been associated with blockage of drainage from the involved area followed by release of the accumulated purulent material with possibly some surrounding lobular pneumonia The terminal phase of the illness may have been due to the development of bacteremia The renal changes may have been caused by metastatic abscesses in the kidney while the *nervous system manifestations* may have been due to similar lesions in the brain However the blood cultures were sterile and there are a few complicating features which make the exploration of other *possibilities necessary*

In the absence of any specific diagnostic findings it is desirable to make a survey of the various causes of rather high fever and leukocytosis

(1) Infections associated with *bacteremia* It is ordinarily easy to obtain positive blood cultures with infections due to streptococci or staphylococci but with other organisms such as the *gonococcus* or the bacteroides group it is more difficult Vegetative endocarditis must always be considered in a patient with possible valvular heart disease and unexplained fever There were no recognizable *embolic* phenomena in this patient but she had anemia splenomegaly and kidney changes which might have been the result of bacterial endocarditis There was a systolic thrill and murmur over the *pulmonic* area Occasionally one sees the picture of a diffuse encephalitis associated with small cerebral emboli which may produce all of the nervous system manifestations and the cerebrospinal *fluid findings* which were exhibited here She could have had pelvic inflammatory disease due to the gonococcus as the possible source of infection

(2) Of the various *localized infections with abscess formation* there may have been a pulmonary abscess or the chronic bronchiectasis

may have given rise to a cerebral abscess A pelvic abscess as the source of a terminal bacteremia seems unlikely on the basis of the evidence at hand

(3) Next we must consider *localized infections without abscess formation* such as pyelitis meningitis or encephalitis This patient was catheterized just before the onset of the high fever and *Escherichia coli* were cultured from the urine The urine became sterile with antibiotic therapy This type of infection would not ordinarily produce such a severe and prolonged systemic reaction particularly when there was no evidence of urinary tract obstruction

If we accept the spinal fluid pleocytosis as evidence of a meningeal reaction there are several possible causes to consider a sterile meningitis associated with brain abscess or some specific inflammatory disease such as tuberculosis Encephalitis also must be considered This might be due to infection or possibly be associated with a diffuse type of connective tissue disease as we shall see later

(4) We must also consider the various types of *specific infection* two in particular—tuberculosis and actinomyosis Amebiasis must be mentioned because of the combination of abdominal and pulmonary involvement but it is quite unlikely Rheumatic fever must also be placed on the list because certain of the features such as cardiac enlargement murmurs leukocytosis and possibly the nervous system manifestations might conceivably be explained on this basis

(5) Diseases of the blood forming organs must always be considered as a possible cause of unexplained fever Sickling of the red blood cells had been noted on occasion but with the terminal illness there was no conspicuous anemia Thrombotic change in small vessels may produce a variety of clinical manifestations but none seems to fit this situation There is no evidence here for lymphoma leukemia or aplastic anemia all of which may be accompanied by a striking alteration in body temperature

(6) A great many *malignant tumors* particularly those of the abdominal organs are accompanied by fever Among the prominent primary neoplasms causing pyrexia are those of the kidney liver bronchus and pleura Although this patient at times had hematuria I think a bronchogenic neoplasm is the only possibility worth further thought and this seems unlikely even though cerebral metastases could explain many of the findings noted during the terminal febrile phase

(7) Finally there is a miscellaneous group of causes which includes toxic agents and products of tissue death—drug fevers pulmonary

and myocardial infarction, and accumulation of blood in body cavities

From the nature and course of the final illness we might be dealing with a reaction to penicillin sulfonamides or streptomycin, or the patient might have had an iodine hypersensitivity reaction associated with the second Lipiodol instillation, leading to the development of acute periarteritis nodosa

Thus of the various causes of fever the following possibilities present themselves for further consideration

(1) Chronic bronchiectasis with pulmonary suppuration leading to bacteremia and a possible brain abscess
(2) Valvular heart disease with vegetative endocarditis
(3) Tuberculosis
(4) Actinomycosis
(5) Rheumatic fever
(6) Carcinoma of the lung
(7) Drug hypersensitivity with acute periarteritis nodosa

Rheumatic fever and carcinoma of the lung for many reasons cannot be seriously considered as a cause of the important features of this case Bacterial endocarditis if present could only be a sequel of the bacteremia due to some more fundamental underlying disease Three major possibilities are left to account for the chronic pulmonary disease

Tuberculosis might account for the localized pulmonary disease particularly if one postulates involvement of the bronchi to the left lower lobe and lingula with partial obstruction In this event one might logically conclude that the terminal febrile illness represented a miliary spread with meningitis appearing just before death There are however certain objections to this conclusion Leukocytosis which was prominent is unusual in *miliary tuberculosis* Furthermore tubercle bacilli carefully looked for on numerous occasions were never found In addition streptomycin seemed to have no influence on the course of the illness

Mycotic infection of the lung such as *actinomycosis* must be considered The early symptoms of this disease are those of a subacute pulmonary infection with cough fever and expectoration which gradually becomes mucopurulent and may contain blood Small abscesses form in the lung frequently invading the pleura and giving rise to pain In the early stages the lesions resemble those of tuberculosis and as the disease progresses areas of consolidation develop

with ill defined patches of rarefaction suggesting abscesses The lesions progress by direct invasion and in the present case invasion of the mediastinum and pleura might have accounted for the pain *Abdominal involvement in the cecal region is not uncommon* and this may have accounted for the symptoms and signs referable to the right lower quadrant Penicillin in very large doses may cure the infection but the amounts this patient received may have served merely to retard its progress Dissemination may occur and the picture of a generalized blood stream infection may eventually develop In brief it is possible that this patient had actinomycosis Enlargement of the liver and spleen might conceivably have been due to amyloidosis as a complication

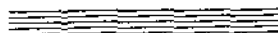
After considering the alternatives I am led finally to conclude that this patient had what she was thought all along to have—chronic *bronchiectasis with pulmonary suppuration* and a terminal bacteremia with cerebral abscess formation and a sterile meningitis In this event the question remains whether or not the terminal high fever with renal and central nervous system manifestations was due to a hypersensitivity reaction to iodine penicillin or sulfonamide with a resulting acute periarteritis nodosa The lack of any bacteriological evidence of a generalized infection and the fact that the fulminating process developed while she was receiving antibiotic and chemotherapy make it likely that this was an allergic reaction to one of these drugs most likely iodine or the sulfonamide

ANATOMICAL DIAGNOSIS (Autopsy No *20859*) *History of sulfonamide therapy* bronchography and acute febrile illness Interstitial myocarditis with collagen degeneration Thrombi in splenic vessels Infarcts and focal necroses in spleen Ependymal glial nodules (ependymitis granulosa) Satellitosis in corpus striatum Tubular bronchiectasis left lower lobe and lingula of upper lobe Focal scarring left upper lobe Fibrous pleural adhesions Lobular pneumonia gram positive cocci Fatty infiltration of liver Chronic cystitis Focal metaplasia of pancreatic duct epithelium Focal dilatation of pancreatic acini

The bronchi in the left lower lobe were dilated but contained no exudate or mucous material The heart appeared normal on gross inspection but microscopic study revealed many foci of mononuclear cell infiltration often associated with swollen collagen fibers Eosinophils were rare The lungs showed lobular pneumonia and purulent bronchitis Some of the bronchi showed mononuclear cell infiltration and scarring of their walls The liver contained a moderate amount of fat There were accumulations of mononuclear cells some of which approached an epithelial type in the periportal spaces There were numerous necroses in the spleen and although a few

fibrin thrombi were seen there was not sufficient thrombosis of vessels to account for the numerous necrotic areas Many hemorrhages were also present The lesion was not typical of sickle cell anemia There were numerous dilated acini in the pancreas The kidneys were essentially normal The myocardial lesions and the splenic necroses were compatible with a hypersensitivity reaction to sulfonamides It was thought clinically that she might have had a reaction to Lipiodol but no evidence of any local reaction was observed clinically nor was any seen pathologically

SUMMARY This 21 year old Negro female who had the hallmarks of sickle cell disease developed bronchiectasis and signs of pelvic inflammatory disease and was admitted for antibiotic treatment Bronchograms were made on two occasions and following the second the patient developed fever malaise meningismus disorientation leukocytosis and finally a slight mononuclear pleocytosis Systematic exploration was made of the various conditions which might have caused this fulminating terminal febrile illness The evidence seemed to support the diagnosis of bronchiectasis complicated by a drug hypersensitivity reaction and the development of acute periarteritis nodosa At autopsy BRONCHIECTASIS was found and there was an interstitial myocarditis with collagen degeneration and multiple areas of necrosis in the spleen In the absence of any pulmonary reaction attributable to Lipiodol it was thought that there was an ALLERGIC REACTION probably due TO THE SULFONAMIDE



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Chapter 14

UNKNOWN CASES FOR STUDY

IN THIS CHAPTER we present eleven case histories apart from the discussion in each instance to give the reader opportunity to make his own analysis of the case and reach a diagnosis It is possible then to turn to the section beginning on page 590 and read there the discussion anatomical diagnosis and summary in each case to learn the correct answer to the diagnostic problem

Case Histories

I

(#392581 Admitted February 23 1947 Died February 23 1947)

This 63 year old Negro male complained of dyspnea and edema On examination at the age of 33 years the lungs were found to be clear The cardiac impulse was diffuse and forceful A systolic murmur was heard at the apex and in the left axilla A similar murmur was audible over the pulmonic area and the pulmonic second sound was accentuated The blood pressure was 150/100

The patient felt well and worked as a laborer until November 1945 when he began to experience anorexia and loss of weight In January 1946 he complained of fatigability and exertional dyspnea The dyspnea grew progressively worse and in March he developed a cough worse at night and occasionally productive of mucoid sputum During the week before his first admission on July 18 1946 his respiratory distress became severe and he had to remain in a sitting position most of the night Three days before admission he developed edema of the ankles

Summary of First Admission (July 18 to August 25 1946) *Physical Examination* T 99 6 P 92 R 24 B P 190/60 There was dyspnea orthopnea and evidence of weight loss There was edema of the lower extremities and over the sacrum The scleras appeared icteric The left pupil was larger than the right but both pupils reacted normally The retinal arteries were narrowed and tortuous The thyroid was not enlarged There was fullness of the cervical veins Moist rales were heard at both lung bases The cardiac dullness was 13 cm to the left in the 5th interspace At the apex the first heart sound was replaced by a blowing systolic murmur The pulmonic second sound was short and sharp In the aortic area both sounds were replaced by murmurs The aortic diastolic murmur was heard over the entire precordium A suggestive Flint murmur was audible in the mitral area The rhythm was regular The peripheral arteries were thickened and tortuous Pistol shot sounds were audible over the femoral arteries The radial pulses were collapsing in type The liver was enlarged and tender The spleen was palpable Neurological examination revealed no abnormalities

Course in the Hospital The temperature fluctuated between 100 and 102 He improved after digitalization and rest in bed The Wassermann reaction was positive and he was given a course of penicillin No Herx

heimer reaction appeared The temperature returned to normal four days after penicillin therapy was begun After the second week in the hospital he felt well was allowed out of bed and was discharged on August 25 1946

Laboratory Data Hemoglobin was 12 5 gm on admission but had dropped to 10 gm at the time of discharge Leukocyte counts and differential counts were within the limits of normal Urine had a specific gravity of 1 016 positive test for albumin a few white cells and an occasional red cell and hyaline cast Phenolsulfonphthalein excretion was 26% in 2 hours Total serum proteins were 7 44 gm % with albumin 2 5 gm / and globulin 4 94 gm % Bromsulfalein test of liver function showed 44% retention at the end of 30 minutes Cephalin flocculation was 3 plus and thymol turbidity 32 units The spinal fluid Wassermann reaction was negative in all dilutions up to 1 0 ml X ray examination of the chest showed extensive clouding of both lung fields thought to be secondary to the cardiac condition There was enlargement of the heart with prominence of the left ventricle X ray of the chest before discharge showed clearing of the congestive changes Electrocardiographic examination showed left axis deviation with changes in the T waves thought to be compatible with digitalis intoxication The precordial leads showed an absent R wave with a deep S and a small T wave suggesting the possibility of an anterior type of myocardial infarction Several blood cultures were sterile

On one examination on July 22 a systolic thrill was felt at the base of the heart and a less intense thrill at the apex The to and fro murmur at the aortic area was unchanged In the 4th and 5th interspaces to the left of the sternum the first sound was preceded by a short crescendo rumble The impression was that he had cardiovascular syphilis with aortic regurgitation and cirrhosis of the liver

The patient continued to have symptoms of mild cardiac insufficiency which increased in severity before his final admission He developed an upper respiratory infection and after this his symptoms were accentuated During the month before admission he had two attacks of sharp substernal pain associated with an increase in dyspnea

PHYSICAL EXAMINATION on final admission T 99 P 95 R 38 B P 190/100

A few crepitant rales were heard at the right lung base The heart was unchanged in size The sounds were of poor quality In the mitral area there was a blowing systolic murmur transmitted into the axilla The diastolic and systolic murmurs at the base had not changed in quality A presystolic sound was heard in the apical area The pulmonic second sound was loud There was ascites and the liver was enlarged The spleen was palpable and tender and a faint crunch could be heard over it There was edema of the legs and over the sacrum

The venous pressure was elevated and the circulation time was prolonged The patient died 8 hours after admission

(For Discussion turn to page 590)

II

(#213063 Admitted October 8 1940 Died October 9, 1940)

THIS 33 year old white housewife complained of pain in the abdomen Ten years previously following an attack of abdominal pain she had been operated on with removal of the appendix and the right ovary and tube For many years she had had urinary frequency and nocturia and for five years her menstrual periods had been irregular There were no symptoms referable to the gastrointestinal tract prior to the current illness

Four months before admission she had a period of severe constipation accompanied by pain in the left lower quadrant of the abdomen This pain was shooting in character and was exaggerated after a cathartic After several days the attack was ended with the passage of liquid stools containing blood and she was then free of symptoms for four weeks During a second similar attack there was a steady ache in the left lower quadrant and episodes of nausea and vomiting She was told that she had salpingitis and was treated with sulfanilamide She had several further attacks of the same character Her appetite was poor and she lost weight rapidly Nausea and vomiting became more frequent The pain in the left lower quadrant was continuous for the week before admission She had had during the preceding few weeks numerous and copious bowel movements At the time of admission the pain was localized to the left lower quadrant and was not aggravated by ingestion of food or by bowel movements

PHYSICAL EXAMINATION on admission T 100 P 100 R 25 BP 120/60

The patient was very obese and appeared to be extremely ill grunting and rolling about in pain There was no cyanosis or edema The skin and mucous membranes were pale The pupils reacted normally and the fundi were not remarkable The teeth were in poor condition The tongue was not red The thyroid was not enlarged The lungs were normal The area of cardiac dullness was not increased No murmurs were heard The breasts showed no abnormalities The abdomen was pendulous No organs or masses could be felt There was tenderness on palpation particularly in the left lower quadrant where there was definite muscle spasm There was no ascites Rectal examination showed tenderness in all areas On pelvic examination there was also tenderness in all areas Neurological examination revealed no abnormalities

COURSE IN THE HOSPITAL A few hours after admission the patient complained of cramping pains in the lower abdomen more severe in the right lower quadrant She had four watery bowel movements which contained no gross blood but gave a strongly positive guaiac test She developed tenderness in the right lower quadrant with muscle spasm and rebound tenderness A catheterized urine specimen was packed with white blood cells and contained an occasional red blood cell but no casts or albumin The leukocyte count was 7 500 It was decided to obtain a flat x ray film of the abdomen in the erect position While standing the patient

suddenly collapsed Her pallor increased the heart rate became very rapid and the blood pressure fell to 90/50 She was incontinent of feces and urine After the administration of intravenous fluid her condition improved and the blood pressure rose to 130/80 She complained bitterly of pain in the right lower quadrant She was sent to the General Operating Room Death occurred under anesthesia

LABORATORY DATA Blood serologic test for syphilis was negative On admission the red blood cells numbered 3 37 million hemoglobin was 9 2 gm hematocrit 31 icterus index 5 sedimentation rate (corrected) 3 mm per hour leukocyte count 11 000 with 1% myelocytes 6% juvenile neutrophils 79% segmented neutrophils 1% monocytes and 13% lymphocytes The blood smear showed no significant abnormalities Urine culture was sterile Stool culture showed no pathogenic organisms

(*For Discussion turn to page 593*)

III

(#493875 Admitted March 14 1949 Died March 17 1949)

THIS 22 year old white chauffeur entered the hospital in coma At the age of 7 years he had had an acute polyarthritis with accompanying subcutaneous nodules At the age of 10 years he had had a recurrence of joint symptoms and a systolic mitral murmur was noted At 12 years he again had active rheumatic fever and a diagnosis of mitral stenosis was made

Two weeks before entry he complained of sudden weakness drowsiness anorexia and crampy abdominal pain The attacks of pain were short in duration and knife like in character He vomited all solid food One week before admission he developed severe and constant frontal headache His abdominal pain disappeared but the vomiting persisted Drowsiness increased and he slept a great deal Four days before entry he looked pale complained of substernal pain and had a feeling of chilliness The morning of admission he was confused and was too weak to dress A few hours later he was unable to talk although he appeared to understand what was said to him He became progressively less responsive and was admitted in a comatose state Two weeks before admission he had handled two skinned muskrats There was no history of drug ingestion or of exposure to any chemicals

PHYSICAL EXAMINATION on admission T 104 P 130 R 36 B P 132/82

The patient was a well developed slender man in coma There was mild icterus Numerous petechiae and a few purpuric areas were noted over the arms shoulders and thorax The respirations were Cheyne Stokes in type There was pallor of the mucous membranes and the nail beds were

cyanotic The pupils reacted normally but the eyes moved aimlessly from side to side No abnormalities were seen on funduscopic examination The nose contained dry blood There was no significant lymphadenopathy There was no cervical rigidity The lungs were normal The left border of precordial dullness extended to the anterior axillary line in the 5th inter space There was also enlargement of the heart to the right There was a systolic thrill at the apex and a diastolic tap was felt in the pulmonic area The first mitral sound was loud and continuous with it was a harsh blowing systolic murmur There was a low pitched apical diastolic murmur Some observers described a diastolic murmur in the aortic area The liver spleen and kidneys were not enlarged There was no edema

COURSE IN THE HOSPITAL The temperature remained between 103 and 105 and there was marked tachycardia A diagnosis of acute bacterial endocarditis was made After blood had been obtained for cultures anti biotic therapy was instituted with penicillin and Aureomycin The patient became more cyanotic and the jaundice increased after a transfusion He never moved his right leg There was persistent twitching of the facial muscles on the right side The day following admission he had severe generalized convulsions He remained in coma the fever persisted and death occurred on the 4th hospital day

LABORATORY DATA Blood serologic test for syphilis was negative Red blood cells were 2 6 million hemoglobin 7 5 gm hematocrit 23 icterus index 12 bleeding time 13 min clotting time normal leukocyte count 10 800 rising later to 20 500 differential count showed 2 5% myelocytes 3% juvenile neutrophils 73% segmented neutrophils 20% lymphocytes 1 5% monocytes platelets numbered 40 000 There was no clot retraction Special studies showed no abnormal circulating anticoagulant Urine examination showed 2 plus albumin 2–4 white cells 15–20 red blood cells and an occasional granular cast per high power field Stools were positive for occult blood Cultures of the blood of material from a petechial lesion urine and spinal fluid were all sterile Blood nonprotein nitrogen was 45 mg % on admission rising subsequently to 67 mg % bilirubin was 2 5 mg % total The first spinal fluid examination revealed 30 mononuclear cells per cu mm the protein content was normal and the serologic test for syphilis negative the second examination two days later revealed pink fluid with 1 000 red cells and only 2 white cells per cu mm

Electrocardiogram on March 15 showed rate 111 P R interval 0 13 sec P waves normal There were a small Q3 and a very large RV5 present T1 was low in amplitude T2 T3 and TV5 were inverted The record was interpreted as showing markedly abnormal T waves suggestive of the possibility of a posterolateral myocardial infarction

Bone marrow examination showed marked polychromatophilia with moderate aniso and poikilocytosis The marrow smears were cellular Megakaryocytes were numerous but showed no evidence of platelet formation The proportion of nucleated red cells was high Otherwise the differential count was normal

X ray of the chest on March 14 showed the heart was greatly enlarged

with increase in the caliber of the vascular markings suggesting passive pulmonary congestion There was no definite evidence of pneumonia

(*For Discussion turn to page 596*)

IV

(#484774 Admitted December 20 1948 Died January 21 1949)

THIS 45 year old white male entered the hospital complaining of pains all over He was known to have had severe hypertension for several years In September 1948 he developed severe pain over the base of the spine which troubled him particularly when he was in the sitting po ition and which remained more or less constant for several days The pain gradually improved over the next two weeks but then he developed a severe catchy pain under both scapulas accentuated by deep breathing and radiating into both shoulders During the next few weeks pain along the spine was severe constant and incapacitating From then until admission he con tinued to have migratory pains involving several regions at the same time including the medial portions of his thighs and legs both hips ankles shoulders back chest abdomen and medial surfaces of his arms The pains were deep and persistent at times causing excruciating agony In November x ray studies of the bones were reported as normal His appetite was poor his weight dropped from 200 to 140 pounds On one occasion his urine was reported as deeply colored During the month before admis sion he had moderate dyspnea which he thought was secondary to the pain

PHYSICAL EXAMINATION on admission T 96 6 P 120 R 28 B P 220/140 in right leg 180/110 in right arm

Even light palpation of any part of the patient s body caused facial grimaces and rapid shallow respirations There was evidence of moderate weight loss and generalized muscular atrophy The mucous membranes appeared pale There was no local or general lymph node enlargement There were no gross skeletal abnormalities Both eyes were prominent with widening of the palpebral fissures A slight lid lag was noted but the extraocular movements were normal The pupils reacted normally The retinal arterioles were narrowed and had a silvery appearance The remain ing teeth were in poor condition many being carious The gums were spongy The pharynx was injected and the tongue was covered with a grayish exudate There was no cervical rigidity The trachea was in the midline The thyroid was not enlarged Movements of the chest were limited but symmetrical The percussion note was normally resonant The breath sounds were distant but vesicular except over the lower anterior thorax on both sides where a slightly tubular quality was noted Inconstant

rhonchi were present over the entire chest anteriorly The bases descended poorly The heart was normal in size A presystolic gallop rhythm was described There was a pulmonic systolic murmur The peripheral arterial pulsations were normal The liver edge was percussed 2 fingerbreadths below the costal margin The genitalia were normal The prostate was moderately enlarged and firm The extremities were normal Neurological examination revealed no abnormalities

COURSE IN THE HOSPITAL On the 11th hospital day the patient developed hallucinations and exhibited transient paranoid trends On the 20th day penicillin was administered because of an elevation in temperature which reached 100 to 103 each day A fusiform swelling was noted along the 5th rib in the right axilla This was moderately tender and firm The x ray examination was believed to demonstrate an interlobar pleural effusion in the right lung but several attempts to obtain fluid from this area were unsuccessful The patient became comatose and died on the 33rd hospital day

LABORATORY DATA Blood serologic test for syphilis was negative Hemoglobin was 13 5 gm hematocrit 42 icterus index 3 sedimentation rate 35 mm per hour Total leukocyte count ranged from 8 200 to 35 450 The differential count showed an occasional myelocyte juvenile neutrophils varying from 2 to 7% segmented neutrophils varying from 68 to 85% eosinophils 1% an occasional basophil lymphocytes varying from 5 to 22% and monocytes from 1 to 7% Platelets were plentiful Stool examinations were negative for blood Blood nonprotein nitrogen was 41 mg % on admission rising to 93 mg % before death CO_2 combining power 26 6 mEq chlorides 101 mEq serum protein 6 8 gm % with albumin 4 2 gm % and globulin 2 6 gm % cholesterol 200 mg % Three determinations of serum calcium varied from 11 to 12 8 mg % phosphorus from 4 2 to 4 7 mg % alkaline phosphatase activity 6 5 Bodansky units Determinations of basal metabolic rate ranged from plus 40 to plus 67 Cultures of blood urine and stool showed no significant organisms Urinalysis showed specific gravity from 1 013 to 1 024 sugar negative occasional 1 plus albumin Microscopic examination occasionally showed a few white blood cells a rare red blood cell and occasional granular casts No Bence Jones protein was demonstrated Phenolsulfonphthalein excretion was 65% in two hours Tuberculin skin test (2nd strength PPD) showed a 2 plus reaction Bromsulfalein excretion was normal Prothrombin time was 26 sec approximately 50% normal activity Agglutination tests and blood cultures for Brucella were negative Electrocardiogram was normal Biopsy of muscle showed no significant lesions

On December 21 chest x ray showed considerable elongation of the aorta and prominence of the aortic knob There was a slight homogeneous clouding in the region of the right middle lobe which was suggestive of a pneumonic process

On December 26 a gastrointestinal series showed stomach and duodenum normal Cholecystogram showed the gallbladder concentrating the opaque medium well there was no evidence of stone X ray of the cervical thoracic and lumbar spine showed no significant lesions

X ray of the chest on December 28 showed evidence of pleural fluid between the right middle and right lower lobe in the greater fissure line and infiltration in the posterior portion of the right lower lobe In x ray of the skull there were no areas of destruction or new bone formation On January 11 chest x ray showed slight increase in the interlobar pleural effusion between the right lower and middle lobes and slight increase in bronchovascular markings bilaterally particularly at the bases

Spinal fluid had an initial pressure of 140 mm water and showed good response to jugular pressure One white blood cell was seen Sugar was 68 mg % chloride 119 5 mEq /L protein 79 mg % colloidal mastic test 2211000000

(*For Discussion turn to page 600*)

V

(MIBH #47677 Admitted December 13 1952
Died January 1 1953)

THIS 29 year old white male filling station attendant first came to the hospital in January 1951 complaining of high blood pressure The family history was of interest in that his mother aged 61 years had hypertension In the past he had enjoyed excellent health There was no history of hematuria edema scarlet fever rheumatic fever acute nephritis cystitis or pyelitis He was in excellent health while serving overseas with the United States Army during World War II He had had an appendectomy in 1942

Although the present illness presumably began in the latter part of 1950 there were earlier symptoms which may have been related At the age of 19 years one year prior to his appendectomy he began to have occipital headaches usually upon awakening in the morning and occurring once or twice weekly for a 10-year period These headaches had not been severe enough to interfere with his activities When discharged from the Army in 1946 he presumably had normal blood pressure and normal urinalysis Since 1946 he had had nocturia 1 to 3 times nightly About 1948 he noted easy fatigability but lost no time from work In July 1950 when donating blood for the Blood Bank his blood pressure was recorded as 124/78 On January 18 1951 he was rejected as a blood donor because of hyper tension This prompted him to seek medical advice During his first hospital admission January 21 to 29 1951 the casual blood pressures varied from 220/145 to 160/120 In the cold pressor test the blood pressure rose from 180/130 to 222/162 and during sleep induced by Amytal sodium it fell from 185/140 to 140/110 During a piperoxan test pressure rose from 170/120 to 190/130 In addition to the hypertension the physical

examinations revealed thickened rubbery radial arteries and markedly narrowed and beaded retinal arteries Both optic discs were blurred and there were a few retinal exudates The general physical condition was excellent and the patient was alert and intelligent Urine specimens showed 0 to traces of albumin occasional white and red blood cells and a few hyaline and granular casts Specific gravity of casual specimens was 1 010 to 1 015 specific gravity in concentration tests 1 010 to 1 050 Urine cultures were negative Phenolsulfonphthalein excretion was 60% in 1 hour 70% in 2 hours Intravenous pyelograms showed good function on both sides the kidneys were normal in size shape and position The heart was normal in size and shape An electrocardiogram showed widening of the QRS T angle and evidence of left ventricular hypertrophy There was no anemia or leukocytosis Sedimentation rate was 4 mm per hour fasting blood sugar 67 mg % blood urea nitrogen 14 5 mg % basal metabolic rate plus 9

After a brief and ineffective course of treatment with low salt diet and veratrum alkaloids he was admitted to the hospital and a bilateral lumbo dorsal sympathectomy was performed in 2 stages on February 27 (left) and on March 16 (right) In both operations the adrenals and kidneys were palpated and no abnormalities could be detected There was no comment about the condition of the renal arteries Convalescence from both opera tions was complicated by partial pneumothorax The operations had no effect on the level of the blood pressure but the patient improved symp tomatically and returned to work

During the ensuing 15 months his blood pressure was constantly at a very high level with diastolic pressure between 120 and 170 In June 1952 there were episodes of acute pulmonary edema The heart was then enlarged to the left There was a gallop rhythm x rays showed engorge ment of the pulmonary vessels

He was admitted to another hospital in July 1952 and remained under treatment there for 4 months The physical examination there was much the same as previously reported except for more extreme changes in the eyegrounds In the initial examination a firm mass was felt in the region of the left kidney Repetition of intravenous pyelograms showed that the kidneys were normal in size shape and position The patient received suc cessive courses of veratrum alkaloids hexamethonium and hexametho nium plus hydralazine hydrochloride During the latter medication the blood pressure fell from an average of 220/170 to 175/120 In September 1952 while the patient was still on these drugs the blood pressure rose again phenolsulfonphthalein excretion diminished and blood nonprotein nitrogen rose to 58 mg % He became weak and anemic and developed peripheral edema and bilateral pleural effusion When discharged from the other hospital November 24 1952 he was still on treatment with hexamethonium and hydralazine his blood pressure was 200/150 albu minuria 4 plus blood nonprotein nitrogen 73 mg % CO_2 combining capacity 18 2 mEq /L

About December 10 1952 he developed dyspnea and cough which became progressively worse On December 12 he had chilly sensations

and his temperature was 102 The following day he was readmitted to this hospital

PHYSICAL EXAMINATION on final admission T 101 6 P 86 R 26 B P 210/160

The patient was thin pale restless dyspneic and orthopneic There was edema of the lower trunk and legs There were advanced retinitis with marked narrowing of the retinal arteries papilledema hemorrhages and exudates Dullness and rales were noted at both lung bases Heart was enlarged to the left and there was a presystolic gallop A tender liver edge was palpated at the level of the umbilicus No mass was felt in region of kidneys Strong arterial pulses were felt in the legs and feet

COURSE IN THE HOSPITAL Temperature rose to 103 to 104 the first 2 days then gradually fell to reach normal on the 5th day Blood pressure continued very high blood urea nitrogen fell from 107 mg / to 76 mg / in one week and then rose again reaching 182 mg % on December 31 In the last few days of his life the patient became increasingly lethargic and more edematous and developed a pericardial friction rub

LABORATORY DATA Hemoglobin was 8 6 gm leukocyte count 5 150 with 85/ polymorphonuclears Urine had a specific gravity of 1 008 to 1 014 albumin 2 plus to 4 plus rare white and red blood cells and hyaline and granular casts Blood urea nitrogen was 107 mg / sodium 140 mEq potassium 3 2 mEq chloride 95 mEq CO combining capacity 20 1 mEq calcium 4 1 mg / phosphorus 12 5 mg X rays of the chest showed engorgement of pulmonary vessels and fluid in both pleural cavities Electrocardiograms again disclosed widening of QRS T angle and left ventricular hypertrophy

(For Discussion turn to page 603)

VI

(MIBH #46761 Admitted February 9 1951
Died February 26 1951)

THIS 52 year old white housewife entered the hospital complaining of severe headache and nausea She had had 4 operations (1) thyroidectomy in 1930 for symptoms which were attributed to hyperthyroidism (2) hysterectomy in 1935 for the relief of dysmenorrhea (3) cholecystectomy in 1941 for gallstones (4) removal of a hard tumor from the roof of the mouth in 1949 This tumor had been present for at least 20 years and was said not to be malignant She had always been subject to frequent headaches accompanied by tinnitus There was no history of rheumatic fever or cardiac disease

The present illness began insidiously In 1945 there was painless swelling of the ankles which subsided after treatment with some sort of pills Early in 1949 there was painful swelling and stiffness of multiple joints The knees particularly were swollen red painful and so stiff that she had difficulty in walking The hips lower back arms hands and shoulders were similarly involved The pain was not relieved by salicylates She was treated with thyroid hormone with some apparent improvement The patient had also noted episodes of numbness tingling and blanching of the fingers and toes especially when exposed to cold With the passage of time the skin over the fingers cheeks and neck had become stiff and tight In February 1950 she developed painless swelling of the ankles similar to that experienced in 1945 but on this occasion the swelling spread upward to involve the legs and abdomen On a low salt diet and with injections of mercurials the swelling gradually subsided in a period of 2 months

SUMMARY OF FIRST ADMISSION (October 16 to November 17, 1950)

Physical Examination There was no fever or tachycardia Blood pressure was 130/75 The skin of the face looked puffy and smooth The skin of the hands feet knees and chest felt cool had a mottled reddish blue appearance and felt thick and tough There was periodic blanching of the tips of the fingers and toes The heart was slightly enlarged to the left and there was a moderately harsh apical systolic murmur Many of the joints were stiff and painful on motion

Laboratory Data Red blood count was 3 9 million hemoglobin 11 2 gm leukocyte count 7 000 with normal differential sedimentation rate 24 mm per hour fasting blood sugar 85 mg % blood urea nitrogen 10 0 mg % serologic test for syphilis negative alkaline phosphatase 2 2 King units total serum protein 5 5 gm % with albumin 3 1 gm % and globulin 2 4 gm % No cryoglobulins could be demonstrated Serum cholesterol 190 mg % Urine had a specific gravity of 1 002 to 1 006 otherwise negative Stool was guaiac negative Basal metabolic rate determined twice was plus 1 and plus 37

X ray examination disclosed a moderately enlarged heart which had a flaccid appearance in fluoroscopic examination Study of the esophagus showed delayed passage of barium through the lower esophagus where no peristalsis could be seen X ray pictures of the cervical and lumbar spine showed nothing except slight scoliosis Electrocardiogram showed low T waves over the left ventricle Lumbar puncture showed initial pressure 170 mm water dynamics normal cerebrospinal fluid cell count and chemistry normal Biopsy of skin from the dorsum of the left wrist was interpreted as scleroderma atrophic stage There was striking hypertrophy of the connective tissue the collagen fibers being compressed into dense compact collagenous masses A small arteriole showed thickening of its wall by dense collagenous tissue

SUBSEQUENT COURSE During the patient s stay in the hospital she complained chiefly of headaches She received adrenocorticotropic hormone from October 19 to November 8 the average daily dose being about 30 mg On November 8 she was started on cortisone 100 mg daily Cortisone 50 mg daily was prescribed at the time of her discharge from the

hospital She continued to take this until 10 days before her final admission Between the two periods of hospitalization there was some improvement in the condition of the skin but the patient continued to have severe headaches and her blood pressure gradually rose About two weeks before the second admission she developed pain in the left groin radiating around the left hip During the same period she was also nauseated although she did not vomit

Physical Examination on final admission T 99 2 P 88 R 22 B P 184/92

The skin felt softer but the general appearance of the affected areas was unchanged The face appeared to be more rounded A fluffy exudate was noted in the right optic fundus Sticky rales were heard at both lung bases The cardiac apex was in the 5th intercostal space in the anterior axillary line The first sound at the apex was accentuated The pulmonic second sound was not accentuated There was a questionable presystolic murmur at the apex and a palpable thrill Moderate pitting edema of ankles Good peripheral pulses in the hands and feet No limitation of movement of the joints

Laboratory Data Red blood count 4 3 million hemoglobin 12 3 gm leukocyte count 4 900 with normal differential hematocrit 40 sedimentation rate 18 mm per hour Fasting blood sugar was 61 mg % blood urea nitrogen 16 3 mg % serum sodium 139 mEq potassium 3 9 mEq chloride 102 mEq

The urine in each of 6 examinations had a specific gravity of 1 015 there was no albumin in the first two specimens but there was an increasing amount of albumin thereafter reaching 2 plus before death Microscopic examination was negative except for a few hyaline casts

X ray film of the chest showed marked cardiac enlargement The heart appeared unusually round A second film taken 5 days before death showed that the heart was even larger The pulmonary vessels appeared engorged and there was fluid in the right pleural cavity

An electrocardiogram showed that the T waves over the left ventricle were of low voltage The Q T interval was prolonged

Course in the Hospital Severe headache was the predominant complaint This was sometimes accompanied by stiffness of the neck There was considerable retching and vomiting of small amounts of material On the 5th hospital day the blood pressure rose to 210/125 and the headache grew worse the following day there was a brief tonic convulsion with incontinence of urine A similar convulsion occurred on the 7th hospital day At this time bilateral papilledema was noted A lumbar puncture disclosed an initial pressure of 430 mm water 198 crenated red cells per cu mm protein 77 5 mg % After this the temperature gradually rose and the pulse became quite irregular owing to both auricular and ventricular premature contractions The blood pressure remained elevated the diastolic pressure reaching a peak of 138 on the 10th day Guaiac test on the feces was 4 plus Leukocyte count rose to 19 300 with 84% polymorphonuclear cells The neck veins became distended the dependent edema increased The liver became palpable 3 fingerbreadths below the costal

margin The patient grew increasingly stuporous and on the day of her death was comatose most of the time She passed a number of foul smelling tarry stools Esophageal suction recovered a considerable quantity of dark bloody fluid Prior to death there were signs of bilateral pulmonary consolidation During the last week in the hospital it was noted that she was jaundiced The temperature rose terminally to 105 4° Blood cultures made on February 24 and 26 showed no growth after 10 days

(For Discussion turn to page 609)

VII

(#111687 Admitted April 27 1951 Died April 29 1951)

THIS 67 year old white male complained of shortness of breath pain in the chest and edema of the ankles He had had fever and polyarthritis at the age of 18 years following which he had developed a cardiac murmur In 1931 a diagnosis of emphysema was made It was noted that he had clubbing of the fingers The blood pressure was 140/90 In 1932 a diagnosis of peripheral neuritis was made because of depressed pain sense below the knees and some atrophy of the calf muscles He was seen in 1937 with an acute inflammatory reaction in the right eye with hypopyon A diagnosis of chronic gonorrheal iritis was made and he was treated with sulfanilamide He was seen in 1949 for a recurrence of the inflammatory reaction in his right eye He had a history of moderate alcohol consumption and a rather inadequate diet During the four months before his admission his weight dropped from 147 to 127 pounds

Eight months before admission he noticed shortness of breath when mowing the lawn He had no chest pain ankle edema or difficulty in breathing while at rest Two weeks before entry he had an exacerbation in the shortness of breath developing dyspnea on the slightest exertion He had a dull aching pain in the chest which became worse on exertion and with coughing It felt as though there was a vise on his chest the sensation being beneath the sternum It seemed to be helped by rest He noted edema of his ankles and blueness of his lips He also complained of frontal headache worse when lying down He noticed frequent eructations

PHYSICAL EXAMINATION on admission T 99 P 90 R 20 BP 110/70

The patient was a well developed but poorly nourished man who appeared weak He was moderately orthopneic obviously plethoric and cyanotic The fingers and toes were clubbed There was clouding of the right cornea The left pupil reacted normally to light The left disc was abnormally white No lymph node enlargement was noted There was a smooth round walnut sized subcutaneous nodule to the right of the

suprasternal notch The thyroid was not enlarged The chest was barrel shaped The percussion note was hyperresonant There were fine moist rales at both lung bases posteriorly extending up to the angle of the scapula These were also heard in the axillas The left border of cardiac dullness was in the mid clavicular line There was no palpable or visible precordial impulse The sounds were of good quality and no murmurs were described The liver and spleen were not enlarged The genitalia were normal except for an induration in the left epididymis which felt nodular Rectal examination revealed no abnormalities The reflexes were equal and active

COURSE IN THE HOSPITAL The patient had a low grade fever the temperature on one occasion rising to 101 The blood pressure was low being recorded frequently at 90/60 He was given digitalis The venous pressure was 40 mm of glucose solution The arm tongue circulation time 18 seconds An important laboratory finding was the blood chloride of 86 mEq He remained short of breath and complained of headache He was placed on penicillin It was stated that he swallowed the material that he brought up on coughing The third day he vomited and remained anoretic He complained of hurting all over and had frequent eructations On April 23 he was irrational It was thought that the rapid onset of mental confusion the lack of hallucinations and the relative stability of his behavior in relation to the confusion suggested an organic brain lesion rather than a toxic delirium The spinal fluid was normal It was learned that he had been vomiting for a week prior to admission On April 26 his shortness of breath increased and oxygen was administered He was extremely cyanotic whenever the oxygen was discontinued Although he was given salt by mouth and occasional saline infusions his serum chloride remained low The nonprotein nitrogen was never elevated On April 29 when taken out of the oxygen tent temporarily he had extreme respiratory distress and bubbling rales were heard up to the apices The respiratory rate was 40 and the pulse rate 120 An electrocardiogram showed auricular fibrillation On the day of death he became extremely cyanotic with rapid shallow respirations

LABORATORY DATA Red blood cells numbered 4 78 million hemoglobin 15 gm hematocrit 49 icterus index 3 sedimentation rate 18 mm per hour leukocyte count on admission 12 900 ranged from 21 600 to 32 200 just before death Differential count showed 2% juvenile neutrophils 84% segmented neutrophils 5% eosinophils 1% basophils and 8% lymphocytes Urine examination was normal Stool examination showed no blood or parasites On April 18 blood nonprotein nitrogen was 25 mg % fasting blood sugar 80 mg % CO combining capacity 28 7 mEq chlorides 86 mEq /L total serum protein 4 9 gm % with albumin 2 9 gm % calcium 9 1 mg % phosphorus 3 mg % cephalin flocculation 0 thymol turbidity 3 8 units sodium 131 mEq potassium 4 3 mEq On April 28 blood nonprotein nitrogen was 36 mg % CO -combining capacity 23 7 mEq chloride 84 6 mEq sodium 124 2 mEq potassium 4 4 mEq Eosinophils were 11 per cu mm Vital capacity was 2 05 liters Sputum culture showed growth of numerous alpha and gamma streptococci few pneumococci and beta streptococci Tuberculin test (1st strength PPD) was positive

Electrocardiogram on April 17 showed rate 80 left axis deviation normal record On April 18 there was auricular fibrillation with a rapid ventricular response On April 21 there were evidences of digitalis effect and auricular fibrillation

On x ray of the chest on January 14 1949 the lung fields were clear and there was minimal bilateral emphysematous change On April 17 1951 the heart appeared to be increased in its transverse diameter The aorta was dilated and tortuous The hilar shadows were exaggerated Congestive changes were seen throughout both lung fields and what appeared to be pleural effusions were seen in both bases On April 27 there was a striate and reticular type of mottled density involving the entire left lung field and the lower two thirds of the right lung field The extreme upper portion of the right lung was relatively clear The increase in density of the lung fields was slightly more pronounced at the bases The minor fissure on the right was thickened On April 29 the diffuse mottling over the entire left lung field particularly in its lower half was again noted and there was a diffuse ground glass type of opacification over the lower two thirds of the right lung field X ray of the hands showed no abnormalities of the bones or soft tissues

(For Discussion turn to page 614)

VIII

(#290930 Admitted May 10 1943 Died May 12 1943)

THIS 43 year old Negro woman entered complaining of epigastric pain and vomiting of blood There was no history of any prior digestive symptoms except for an occasional tarry stool over the previous five years

Six days before admission she developed a dull epigastric pain which was aggravated by eating or drinking The pain became so sharp while eating that she could not tolerate food The pain radiated posteriorly to both costovertebral angles It gradually increased in intensity and continued to be aggravated by ingestion of food Shortly before admission she had a paroxysm of coughing followed by profuse vomiting of blood

PHYSICAL EXAMINATION on admission T 99 4 P 110 R 18 BP 40/0

The patient was so ill that only a minimal examination could be carried out The skin was cold and clammy There was marked pallor The tongue was heavily coated The trachea was in the midline there was no tug The lungs were clear to percussion and auscultation The heart was normal in size sounds were faint There was a loud systolic murmur over the entire precordial area No diastolic murmur was heard The abdomen was soft and obese There was tenderness on gentle pressure in the mid-epigastrium

No masses or organs were felt The reflexes were hypoactive No peripheral pulsations could be felt

COURSE IN THE HOSPITAL After the administration of plasma and whole blood the patient s blood pressure rose to 125/65 A few hours after admission she vomited 1200 ml of blood Her pressure then fell to 50/0 and after another transfusion rose to 105/65 During the next few hours the patient had two further hematemeses of approximately 400 ml each

An exploratory laparotomy was performed An incision was made from the xiphoid to the umbilicus After aspiration of large quantities of blood from the stomach no bleeding point could be demonstrated It was decided to ligate the veins along the greater and lesser curvatures of the stomach from the cardiac end to the pylorus The patient was on the operating table for two hours

A few hours after operation she began again to vomit blood and was soon in shock In spite of transfusions she died the following day

LABORATORY DATA Blood serologic test for syphilis was positive Red blood cells numbered 3 08 million hemoglobin 9 5 gm hematocrit 31 icterus index 7 5 sedimentation rate (corrected) 15 mm per hour smear normal Leukocyte count was 12 600 with 2% myelocytes 7% juvenile neutrophils 60% segmented neutrophils 1% eosinophils 1% basophils 27% lymphocytes and 2% monocytes Blood nonprotein nitrogen was 40 mg % albumin 4 31 gm % and globulin 2 63 gm %

(*For Discussion turn to page 617*)

IX

(#430844 Admitted October 9 1947 Died October 21 1947)

THIS 34 year old white housewife entered with severe cough of two weeks duration Her mother died of heart trouble late in life One sister had heart trouble type unknown The patient had had attacks of grand mal epilepsy beginning at the age of 6 years and before that time had been told she had a bad heart During her childhood she had some exertional dyspnea There was no history of joint involvement but at the age of 10 years she had had chorea

Nine months before admission she began to lose weight and her dyspnea increased Two months before admission the dyspnea became even more marked and she had episodes of pain over the left chest following exertion The pain was sharp and would last for several hours She also noted swelling of the ankles and nocturnal dyspnea A diagnosis of aortic and mitral valvular disease was made and she was put on digitalis and a low salt diet Her symptoms improved until two weeks before admission when she developed a severe cough with night sweats and

marked weakness One week before admission she fell out of bed and hurt her left chest For the two weeks before entering she had had frequent bouts of nausea and vomiting particularly after meals

PHYSICAL EXAMINATION on admission T 102 P 96 R 44 BP 110/80

The patient was dyspneic and orthopneic There was a brownish hue to the skin and a malar flush No lymph node enlargement joint abnormalities cyanosis or jaundice was noted The pupils reacted normally The fundi were clear No petechiae were seen The pharynx was normal and the thyroid was not enlarged The right diaphragm descended poorly and there was dullness over the right lung base extending up to the scapula There were scattered rales over the lung bases The cardiac dullness was 15 cm to the left in the 6th interspace There were frequent premature beats There was a loud systolic murmur which was transmitted to the neck vessels and a blowing diastolic murmur was heard in the 3rd interspace to the left of the sternum The 1st sound in the mitral area was loud and was preceded by a diastolic rumble There was a loud systolic murmur at the apex The liver edge was felt 4 fingerbreadths below the costal margin The spleen was easily palpable There was no edema

COURSE IN THE HOSPITAL The patient was extremely ill and during the first week had a temperature between 101 and 104 with a relative bradycardia A right thoracentesis was done on three occasions with removal of 500 700 and 125 ml respectively The usual measures for treatment of cardiac failure were without avail She had a persistent cough which was never productive Because of the fever she was put on penicillin but without any beneficial response After the first week she received acetylsalicylic acid 3 6 gm daily with a dramatic fall in temperature to normal Her extremities remained cold She appeared to be in a state of shock Two days before her death while sitting on the bedpan she had an episode of marked shortness of breath Her pulse was not obtainable for almost a minute and no heart sounds could be heard On the day of death she again requested a bedpan had a similar episode and died

LABORATORY DATA Blood serologic test for syphilis was negative Red blood cells numbered 4 64 million hemoglobin 13 gm hematocrit 32 sedimentation rate (corrected) 32 mm per hour Blood indices and smear were normal Leukocyte count was 13 240 with 6% juvenile neutrophils 82% segmented neutrophils 1% eosinophils 8% lymphocytes and 3% monocytes Subsequent leukocyte counts ranged as high as 23 000

Stool examination was negative for blood and parasites The first urine specimen showed a specific gravity of 1 005 There was 3 plus albuminuria on admission which cleared in five days Microscopic examination showed many white blood cells some in clumps These were not present subsequently No red blood cells were seen Phenolsulfonphthalein test showed 50% excretion in two hours Blood nonprotein nitrogen was 75 mg% sugar 124 mg% bilirubin 3 mg% with 1 6 mg% direct total proteins 7 1 gm% On the day before death the nonprotein nitrogen was 47 mg%

Vital capacity was 600 ml Circulation time (arm to tongue) 21 sec

Venous pressure 200 mm water Several blood cultures showed no growth Sputum cultures showed numerous gram positive cocci in pairs and chains Agglutination tests for tularemia and brucellosis were negative Thoracentesis fluid was straw-colored with specific gravity of 1 010 and 700 white cells per cu mm Culture of the pleural fluid was sterile Bladder culture showed *Aerobacter aerogenes*

Electrocardiogram showed right axi deviation with a prominent notched P2 and a prominent Q3

X ray of the chest on August 8 1947 showed the transverse diameter of the heart was 18 5 cm indicating definite enlargement There was straightening of the left cardiac border with evidence of left auricular and ventricular hypertrophy There were minimal congestive changes with prominence of the vascular markings throughout the middle and upper lung fields on both sides On October 13 1947 the right lung was obscured inferior to the level of the 5th rib The opaque shadow was continuous with the liver shadow inferiorly and with the cardiac shadow medially The appearance was suggestive of a pneumonic process The presence of fluid could not be ruled out

(*For Discussion turn to page 620*)

X

(#601839 Admitted March 27 1952 Died March 28 1952)

THIS 45 year old Polish woman entered the hospital because of vomiting for a period of 9 weeks She had had one pregnancy at the age of 21 years Labor was difficult and the child was stillborn For many years after 1938 she had lived in various concentration and displaced persons camps in Germany It had been noted that her color was sallow for several years

Nine weeks before entry she developed malaise with nausea and vomiting One week before admission there was an increase in the vomiting and in the degree of malaise and weakness There was a vague story of the passage of dark urine and light-colored stools There had been a few nose bleeds No urinary tract symptoms were described

PHYSICAL EXAMINATION on admission T 97 8 P 86 R 30 B P 135/90

The patient appeared chronically ill was dehydrated and had lost weight There was a uremic odor to the breath The mucous membranes were pale The skin was dry and had a yellowish brown appearance Several ecchymoses were noted The posterior pharynx was coated with a yellowish brown tenacious material The tongue appeared smooth along the edges Cotton wool exudates were seen in the left optic fundus and the retinal vessels appeared attenuated The thyroid was twice normal size

The chest had an emphysematous appearance The lungs were clear to percussion and auscultation The heart was not enlarged There was a soft systolic murmur at the apex The abdomen was distended and there was diffuse tenderness of a mild degree which was more marked in the right upper quadrant One observer believed that several nodular masses could be felt throughout the abdomen and that there was shifting dullness in the flanks The reflexes were hyperactive There was ankle clonus and the Babinski reflex was present bilaterally

COURSE IN THE HOSPITAL The patient lived less than 24 hours She was given intravenous fluids and improved temporarily Within a few hours she developed an acute attack of asthma' which improved after phenobarbital and aminophyllin She developed evidences of hyperkalemia with progressive diminution in the activity of her reflexes She appeared to be improving after administration of calcium but suddenly had a convulsive seizure and the pulse became unobtainable

Gynecological examination disclosed normal pelvic organs with no masses in the region of either ureter

LABORATORY DATA Blood serologic test for syphilis was negative Hematocrit 25 icterus index 5 sedimentation rate 30 mm per hour Total leukocyte count was 15 800 Bleeding time was 2½ minutes tourniquet test negative Blood nonprotein nitrogen was 214 mg % sugar 112 mg % calcium 5 5 mg % phosphorus 18 5 mg % bilirubin less than 0 8 mg % CO_2 combining capacity 9 mEq chloride 90 mEq sulfonamide level 0 5 mg % Urine examination showed specific gravity of 1 002 sugar negative albumin negative Microscopic examination of a catheterized specimen showed many red blood cells and pus cells in clumps no casts Urine culture showed *Aerobacter aerogenes* Blood culture showed no growth

Electrocardiogram on March 27 showed a rate of 86 P R interval 0 26 sec left axis deviation QRS complexes normal T waves upright and slightly peaked Interpretation was first degree heart block left axis deviation T waves show evidence of hyperkalemia A subsequent record was interpreted as showing ventricular fibrillation A third record taken after 3 grams of calcium gluconate injected intravenously showed an idioventricular rhythm with wide and varying biphasic complexes with auricular standstill These changes were interpreted as indicative of hypocalcemia and extreme hyperkalemia

(*For Discussion turn to page 623*)

XI

(#125441 Admitted December 11 1951 Died January 15 1952)

This 63 year old Negro was admitted complaining of pain in the right flank In 1932 he had a gonococcal infection The blood pressure was then 188/130 The serologic test for syphilis was negative In 1937 a diagnosis of bilateral infectious arthritis of the sacroiliac joints was made During the next few years the blood pressure varied from 180/126 to 240/160 Urine examination showed no abnormalities He complained at times of pain around his heart and dyspnea at night In 1946 he complained of vomiting dizziness and weakness Examination then disclosed enlargement of the heart the apical impulse being 12 5 cm to the left of the mid line A systolic murmur was described The blood pressure was 190/124 Sclerotic changes were noted in the retinal vessels In 1948 an x ray picture of the spine showed hypertrophic arthritis and an old minimal compression fracture of the third lumbar vertebra The electrocardiogram showed numerous extrasystoles and left axis deviation In February 1949 a perineal prostatectomy was done Biopsy specimens showed no carcinoma In the postoperative period he developed thrombophlebitis and epididymitis

In July 1949 he suddenly developed without loss of consciousness a left hemiplegia left hemihypesthesia and left homonymous hemianopsia Spinal fluid examination revealed a pressure of 170 mm of water normal dynamics protein 144 mg / The Wassermann reaction was negative There were 309 red blood cells and 37 white blood cells per cu mm A faint aortic diastolic murmur was heard The blood pressure was 260/130

In December 1950 he developed paroxysmal attacks of nocturnal dyspnea and had numerous extrasystoles He had complained of back pain for a number of years which became worse after his cerebral accident in 1949 at times radiating down the outside of the left leg to the foot and made worse by movement

On December 10 1951 he complained of severe crampy pains in his hips legs back and right flank The urine showed occasional red cells and white cells with numerous casts There was a 1 plus albumin but no sugar He was thought to have a urinary calculus Deep breathing and movement of the right leg increased the pain in the right flank There was generalized abdominal tenderness The blood pressure was 170/110 There were marked enlargement of the heart frequent extrasystoles and a harsh systolic murmur over the precordium There was evidence of recent loss of weight There was tenderness on palpation in the epigastrium and right costovertebral angle The following day he described the pain in the precordial area as a crushing sensation which radiated down his left arm The blood pressure was 142/100 Moist rales were heard at both lung bases The following day his temperature was normal The blood pressure was 120/80 He appeared sleepy but answered questions with prompting He still complained of pain in the left arm but the precordial and abdominal

pain were less pronounced A friction rub was heard over the precordium On December 21 his temperature rose to 102° rales were heard at the right base the blood pressure was 148/96 there were pain in the right chest and signs suggesting consolidation of the right lower lobe At this time he was transferred from the Surgical to the Medical Service

PHYSICAL EXAMINATION on transfer to the Medical Service T 100 P 100 R 22 B P 160/90

The patient grimaced with pain on movement of the left arm left leg or the spine There was no pain on percussion over the bones There was a left homonymous hemianopsia and marked attenuation of the retinal vessels with arteriovenous compression There was no lymph node enlargement There was an area of tubular breathing at the right base The heart was enlarged to the left There were numerous extrasystoles A pericardial friction rub was noted A systolic murmur was heard in the apical area and at the base where a high pitched diastolic murmur was also audible Radial femoral and popliteal pulsations were palpable There was no venous congestion or edema The abdomen was flat soft and diffusely tender Rectal examination revealed no abnormalities

COURSE IN THE HOSPITAL on the Medical Service The patient had fever and was given streptomycin and penicillin During the next week the temperature reached 103 On December 24 the urine had a specific gravity of 1 010 albumin 2 plus no red cells loaded with white cells occasional granular cast No Bence Jones protein was found Nonprotein nitrogen was 37 mg % and phenolsulfonphthalein excretion was 80% in 2 hours Venous pressure was normal and arm to tongue circulation time was 30 seconds Other blood chemical examinations showed chlorides normal and CO_2 combining capacity 24 2 mEq Total serum protein 9 7 gm % with 2 9 gm % albumin and 6 8 gm % globulin Urine culture showed *A aerogenes*

The patient continued to have pain in the back and legs and on December 26 became less responsive and irrational There was stiffness of his neck and his eyes deviated to the left Lumbar puncture showed opening pressure of 220 mm water fluid clear no cells, negative Wassermann reaction On December 30 he was started on a sulfonamide On December 31 the blood nonprotein nitrogen was 60 mg % It was noted that the urine output was only 450 ml with a fluid intake of 3500 ml He was again disoriented Touching or moving the left arm or leg seemed to cause pain The impression was that his pain was possibly thalamic in origin from his old vascular accident January 2 the nonprotein nitrogen had risen to 85 mg % serum sodium was 127 mEq potassium 3 6 mEq globulin 6 3 gm % The sulfonamide was discontinued From then on the blood nonprotein nitrogen steadily rose reaching 166 mg % on January 7 On January 14 the nonprotein nitrogen was 208 mg % sodium 136 mEq potassium 6 5 mEq calcium 9 8 mg % phosphorus 8 9 mg % and chloride 107 5 mEq On January 12 his urinary output had increased to 850 ml He developed an aspiration pneumonitis on January 12 and three days later was found dead by the nurse

ADDITIONAL LABORATORY DATA Red blood cells numbered 2 85 million hemoglobin 9 5 gm hematocrit 24 icterus index 7 5 sedimenta

tion rate (uncorrected) 67 mm per hour leukocyte count 6 850 with 3% juvenile neutrophils 71% segmented neutrophils 16% lymphocytes and 8% monocytes Two nucleated red cells were seen per 100 white cells There was *no sickling*

Guaiac test on stool blood cultures and blood serologic test for syphilis were all negative

Electrocardiogram on December 17 Rate 97 P R interval 0 16 sec normal sinus rhythm QRS duration 0 12 sec slightly sagging ST1 and V5 *with low upright T waves Interpretation Left axis deviation pro* longed intraventricular conduction time left ventricular strain and/or digitalis effect In subsequent records auricular and ventricular extrasys toles were noted

In x ray examinations made October 5 1948 the gastrointestinal series was *normal* X *ray of the chest showed cardiac enlargement with elongation* and tortuosity of the aorta Spinal x rays showed osteoarthritis of the lumbar spine narrowing of the second lumbar interspace with minimal wedging of the third lumbar vertebra—changes considered compatible with an old compression fracture In February 1949 the chest x ray showed *marked increase in size of the heart with particular prominence of* the left ventricular region moderate elongation and tortuosity of the thoracic aorta Intravenous pyelogram revealed no abnormality although visualization was incomplete A flat plate of the abdomen showed moder ately advanced osteoarthritis of the lumbar spine and a small area of calcification 3 cm *to the left of the* interspace of the 12th thoracic vertebra possibly overlying the upper pole of the kidney A gallbladder series was normal Flat plate of the abdomen showed marked dilatation of the right half of the colon and several loops of small intestine suggestive of a paralytic ileus On December 20 1951 chest x ray showed enlargement of the heart lung fields were clear No bony changes were seen On December 31 x ray of the skull showed the sella base and calvarium within normal limits Films of the pelvis showed some punctate mottling of the bones

(For Discussion turn to page 626)

On the following pages are presented the discussion anatomical diagnosis and summary applicable to each of the eleven cases presented on the preceding pages of this chapter By these the reader may test his own judgment and the accuracy of the diagnosis he was able to reach in each instance

I

(#392581 Admitted February 23 1947 Died February 23, 1947)

(*Continued from page 569*)

DISCUSSION We shall consider first the cause of the heart disease This patient had insufficiency of the aortic valve which because of a weakly positive serologic test for syphilis, was considered to be due to syphilis and was treated as such However one must examine other possible causes for this lesion The description of the heart in 1917 is of particular interest The systolic murmur transmitted to the axillary area and the accentuated pulmonic second sound were suggestive of organic mitral disease It is seldom satisfactory to base a diagnosis on a single physical sign and the position is particularly insecure when the sign is not of a high degree of reliability To say that a constant long harsh systolic murmur heard at or beyond the apical impulse in a young man usually signifies mitral disease and that this conclusion is more reliable when there is a history of rheumatic fever is as strong a statement as can be defended A *positive diagnosis depends on the recognition of mitral obstruction* Evidences of this were described only after the patient had full blown aortic insufficiency and the unreliability of signs of mitral disease in such a situation is well known If there was evidence of aortic stenosis this also would be helpful in making an etiological diagnosis There was a systolic murmur at the base and on one occasion a thrill was felt but there could have been no unequivocal signs of stenosis with such free aortic regurgitation

The changes in the urine and the elevated blood pressure in 1917 may be important He might have had a subsiding acute nephritis at the time following a streptococcal infection In view of the subsequent course of events it seems unlikely that he had repeated attacks of rheumatic activity The rapid progression of the symptoms of cardiac insufficiency once they began is certainly in favor of syphilitic aortic valve disease

If he had rheumatic disease of the aortic valve in 1917 it is con ceivable that stenosis was present at that time and that something took place later to increase the degree of insufficiency The weight loss in spite of edema accumulation the fever which disappeared after penicillin the slight anemia the palpable spleen and the per sistent hematuria suggest that *bacterial endocarditis* may have been the added factor However no petechiae were described and several blood cultures showed no growth Two other possibilities must be considered a syphilitic lesion superimposed on rheumatic aortic stenosis or the development of arteriosclerotic changes in the valve Arteriosclerosis is often advanced as the cause of aortic insufficiency in patients past 50 years of age but if these patients are followed to autopsy many of them are found to have other types of disease

This case affords an example of the difficulty presented by a wide variety of manifestations which must be evaluated and placed in their proper relationships Fever weight loss in spite of edema formation changes in the urine changes in the lung fields enlargement of the liver and spleen reversal of the albumin/globulin ratio all presented problems to those taking care of this patient They form a hetero geneous group of observations most of which could be explained on the basis of heart failure alone Fever is a common accompaniment of severe cardiac insufficiency being the result of a reduction in the efficiency of heat dissipation The poor appetite and altered digestive efficiency associated with chronic passive congestion of the intestinal tract might have been responsible for the loss of weight Edema in chronic cardiac failure is not uncommonly on a nutritional basis with lowered serum albumin Chronic passive congestion of the liver may be indistinguishable clinically from cirrhosis being associated with low serum albumin splenomegaly and impairment of tests of liver function The reduction in kidney function was more than one would anticipate on the basis of heart failure alone but renal arterio-sclerosis might have been a contributory factor

The key to the problem seems to lie in the determination of the cause of the aortic insufficiency In the presence of a positive Was

sermann the answer would appear to be simple Moreover the course of the illness after the development of the first evidence of heart failure was quite characteristic of syphilitic aortic disease relentless progression to a fatal termination without the intermissions of re stored compensation that are so common with rheumatic heart dis ease In view of the past history there might conceivably have been two diseases—syphilitic aortic disease and rheumatic mitral disease From the record it certainly seems likely that he had mitral valvular disease 30 years previously Considering all these possibilities I am inclined to believe that he had rheumatic disease of both the aortic and the mitral valve and that at a later date something happened to increase the degree of aortic insufficiency and to precipitate cardiac failure This might have been caused by syphilis arteriosclerosis, or bacterial endocarditis In spite of the negative blood cultures the weight of the evidence seems to favor rheumatic disease of the aortic and mitral valves with a superimposed bacterial endocarditis

ANATOMICAL DIAGNOSIS (Autopsy No 20438) Healing bacterial endocarditis (gram negative cocci) of aortic valve with extension to ven tricular septum and mitral valve and perforation of aortic cusp of mitral Aortic insufficiency Old infarct spleen Acute splenic tumor Generalized arteriosclerosis and arteriolosclerosis Arteriosclerotic and slight embolic nephritis History of hypertension Cardiac hypertrophy Marked chronic passive congestion lungs and liver Slight pulmonary edema

The aortic cusp of the mitral valve showed a patch of roughening of its auricular surface near which were several pale vegetations What remained of the posterior cusp showed a perforation about 5 mm from its margin The valve about the perforation was thickened and showed some irregu larity resembling bacterial vegetation On the posterior aortic valve leaflet there was a soft vegetation

Microscopically the lesion of the aortic valve showed a healing endo carditis There were bacterial colonies near the surface of the vegetation These were gram negative cocci The fact that this process involved pri marily the aortic valve which was neither bicuspid nor the site of previous endocarditis make it likely that they were gonococci

The final conclusion was that the patient had a gonococcal endocarditis engrafted on previously normal valves

SUMMARY This 63 year old Negro man was found at autopsy to have what was considered to be a healing GONOCOCCAL ENDOCARDITIS engrafted on a normal aortic valve Anorexia and loss of weight were the only symptoms that preceded the onset of cardiac insufficiency Many of the characteristic clinical features of bacterial endocarditis were missing and blood cultures were sterile Manifestations which pointed toward the correct diagnosis were mild unexplained fever anemia and a favorable response to the penicillin which was given because of a positive serologic test for syphilis In attempting to solve this complex problem the discusser

arrived at a correct diagnosis of bacterial endocarditis through a fortuitous process of analysis based upon a false premise The history of a systolic murmur when the patient was 33 years old led the discusser to conclude that the primary cardiac disease was rheumatic valvulitis He believed that the sudden and irreversible cardiac failure was best explained by a super imposed bacterial endocarditis The autopsy disclosed no evidence of rheumatic heart disease and provided no explanation for the systolic mur mur heard 30 years before

II

(#213063 Admitted October 8 1940 Died October 9 1940)

(*Continued from page 571*)

DISCUSSION (The results of the surgical procedure were unknown to the discusser) In the present case there is no clear cut objective finding which will serve to orient the analysis The diagnosis will de pend upon the interpretation of the history and the course of the illness The symptoms including constipation pain in the left lower quadrant nausea and vomiting followed by diarrhea and intestinal bleeding suggest that there was partial obstruction and ulceration of the large bowel The fact that throughout the illness except at the very end the pain was located in the left lower quadrant suggests that the lesion causing this obstruction was located in the descending colon or the sigmoid If this should be the correct interpretation of the functional disturbance which this patient presented then we must review the possible *causes of obstruction of the lower bowel* These may be divided into three main categories

(1) Those due to mechanical causes
(2) Those due to inflammatory diseases
(3) Those due to tumors

The patient had an extensive pelvic operation ten years before her final illness This might furnish a basis for the formation of abdom inal adhesions Occasionally following abdominal operations intes tinal obstruction occurs when a portion of the bowel slips under a band of adhesions with resulting strangulation Such an event may occur many years after the operation During the interval there are often recurring abdominal symptoms before a serious degree of ob struction develops Furthermore the obstruction is most frequently

in the small bowel I cannot remember seeing one in which the large bowel was involved although this may happen In this patient such an explanation seems unlikely Her abdominal symptoms steadily increased in severity and were accompanied by the appearance of blood in the stool, loss of weight and anemia

Next we have to consider *volvulus*, which was the preoperative diagnosis This again comes on suddenly and does not produce illness over a period of months such as this patient had Had she had only the final attack then this diagnosis might be more seriously entertained but under the circumstances it seems only remotely possible The same objection may be made to the diagnosis of acute *intussusception* which is of rare occurrence in adults Chronic intussusception is more common in adults occurring usually in the presence of a tumor or Meckel s diverticulum If this patient had some type of *hernia* which rarely involves the descending portion of the large bowel I can see no way to make the diagnosis on the basis of the information available to us

Among the inflammatory causes of large bowel obstruction two must be considered (a) *diverticulitis* and (b) *ulcerative colitis* With diverticulitis patients may have recurring attacks of obstruction Initially these may be due to infection and edema later they may be caused by adhesions or by angulation of the bowel Such attacks are usually accompanied by systemic evidence of infection This was not a feature of the present case With regard to the second possibility the history does not suggest ulcerative colitis The illness started with severe constipation and abdominal pain diarrhea came only as the episodes of constipation were subsiding I think it altogether unlikely that an acute inflammatory disease was responsible for this patient s illness

All of the manifestations seem to be consistent with the view that the obstruction was due to some type of tumor Furthermore since there was evident intraintestinal bleeding it would seem reasonable to conclude that the tumor had an ulcerated surface within the intestinal lumen The tumors which seem to be the most likely causes of the bowel obstruction in this case are the following

(1) In certain instances *tuberculosis* leads to the production of a dense fibroid mass which causes partial intestinal obstruction without the usual manifestations of active infection Such masses usually involve the cecum and may give rise to recurring attacks of transient and incomplete obstruction These lesions may be mistakenly diag

nosed as carcinoma the final differentiation being made only after examination of microscopic sections The obstruction in the present case was in the descending colon where this type of lesion rarely occurs

(2) Sometimes *lymphosarcoma* begins in the intestines and causes obstruction It might I suppose involve the large bowel but I have never seen such an instance

(3) Characteristic symptoms of obstruction usually without bleeding occur in *regional ileitis* This disease is not strictly limited to the ileum as the name would imply but it is certainly extremely uncommon in the descending colon

(4) The gradual onset of obstruction without evidences of inflammation the bleeding and the loss of weight and strength are all quite characteristic of *carcinoma of the colon* The only objection to this diagnosis arises from the age of the patient However as we have seen in these conferences carcinoma is by no means rare at this age Since everything else seems to point to this diagnosis my final conclusion is that the patient had a carcinoma of the descending colon

The cause of the terminal event which led to the emergency operation must be explained She developed cramping pains over the abdomen more severe in the right lower quadrant and there was tenderness with muscle spasm This would certainly suggest that the colonic lesion had leaked with resulting peritonitis

ANATOMICAL DIAGNOSIS (Autopsy No 17110) Adenocarcinoma of sigmoid colon with partial obstruction Dilatation and hypertrophy of colon above tumor Small ulcers in hypertrophied colon Fistula between jejunum and colon abdominal adhesions Exploratory laparotomy wound Obstruction of larynx by stomach contents (vomiting and death under anesthesia) Large embolus (fresh thrombus) right pulmonary artery Organizing thrombi in small pulmonary arteries Cardiac dilatation Localized nodular scarring mitral valve Few minute scars in myocardium Encapsulated caseous tubercles upper lobe right lung and tracheal lymph nodes Cholelithiasis small cysts right ovary Extreme obesity Fatty liver

The patient died while under anesthesia for the surgical operation The laparotomy disclosed no leakage of intestinal contents into the peritoneum Evidently the collapse during preparation for x ray examination had been due to the large pulmonary embolus Prior to autopsy there was apparently postmortem disruption of the jejunocolic fistula for there was gas in the peritoneal cavity and in the left abdominal gutter there was 500 ml of yellowish brown foul smelling material but there was no evidence of peritonitis There was a perforation 1 cm in diameter in the jejunum 6 inches below Treitz ligament There were two large perforations in the

sigmoid about 18 inches below the hepatic flexure and these were in the center of the constricting tumor which appeared to extend over a distance of 20 cm

The right pulmonary artery contained a long elastic clot which could be pulled out readily The heart weighed 430 grams The right ventricle was moderately dilated

The tumor in the colon was a papillary adenocarcinoma causing partial obstruction with dilatation and hypertrophy of the colon above The coiled blood clot found in the right pulmonary artery was microscopically a very fresh thrombus The site of origin of the embolus could not be determined

SUMMARY This 33 year old white housewife over a period of 4 months had gastrointestinal symptoms which were interpreted as being due to partial obstruction of the descending colon or sigmoid After discussion of the mechanical inflammatory and neoplastic causes of obstruction of the lower bowel it was concluded that a carcinoma of the colon offered the best explanation of the symptoms New symptoms which developed shortly before death were attributed to a perforation of the bowel proximal to the obstruction The diagnosis of CARCINOMA OF THE COLON *was confirmed at autopsy but the terminal event was found* to be due to a large PULMONARY EMBOLUS

III

(#493875 Admitted March 14, 1949 Died March 17 1949)

(*Continued from page 573*)

DISCUSSION Let us first review the important facts about this patient s illness

(1) The final acute illness ran its course to a fatal termination in a period of approximately three weeks

(2) The essential findings were

 (a) A history of rheumatic fever and physical evidence of chronic mitral valve disease,

 (b) Intermittent epigastric pain nausea and vomiting

 (c) Headache drowsiness, aphasia coma and convulsions without clinical meningitis

 (d) Evidence of renal involvement and azotemia,

 (e) Severe anemia with mild jaundice

 (f) High fever and leukocytosis with essentially normal differential blood count

(g) Severe purpura with thrombocytopenia, prolonged bleeding time absent clot retraction and *normal clotting time*

The best documented feature of this patient s illness which can serve to orient the discussion is the thrombocytopenic purpura

The *causes of thrombocytopenic purpura* may be divided into two major categories

- (I) Essential or primary purpura hemorrhagica (Werlhof's disease)
- (II) Symptomatic purpura occurring as a part of some other disease process
  - (A) Following the use of or exposure to a variety of agents which exert a toxic effect or to which a hypersensitivity reaction develops
    - (1) Chemicals and drugs such as arsenic barbiturates gold benzol quinine ergot bismuth iodine hair dyes sulfonamides probably chloramphenicol aniline TNT colloidal silver trimethadione, and propylthiouracil
    - (2) Sensitivity to certain foods or food products such as orris root
  - (B) Following various forms of radiation
  - (C) During the course of certain infections such as various types of bacteremia rickettsial infections bacterial endocarditis meningococcal and gonococcal infections typhoid fever scarlet fever measles smallpox vaccinia chickenpox plague yellow fever undulant fever pneumonia infectious mononucleosis influenza malaria acute hepatitis and rheumatic fever
  - (D) During the course of certain disorders involving the blood forming organs such as
    - (1) Leukemia
    - (2) Aplastic anemia
    - (3) Anemia due to bone marrow replacement by
      - (a) tumor
      - (b) osteosclerosis
    - (4) Splenic involvement
      - (a) portal hypertension
      - (b) Gaucher s disease
      - (c) Hodgkin s disease
      - (d) sarcoidosis
      - (e) so-called primary hypersplenism

(f) splenic vein thrombosis

(g) tuberculosis of spleen

(E) In acute purpura with platelet thrombi in the capillaries—so called thrombotic thrombopenic purpura

(F) As a manifestation of systemic lupus erythematosus

The diagnosis of idiopathic purpura should be made only when one can find no evidence of any condition to which the purpura may be secondary therefore we should first consider the diseases which may produce symptomatic purpura

A thorough investigation was made in this case to determine any exposure to toxic chemical agents but none could be uncovered Nor was there evidence of exposure to any type of radiation

The list of infections which at one time or another have been reported to be complicated by thrombocytopenic purpura is a long one It is true that purpura may follow an acute infection but severe purpura is rare as a dominant manifestation early in the course of the disease The diagnosis when this patient entered the hospital was bacterial endocarditis and there are certain features which suggest this However it is unusual in a fulminating case not to be able to grow the organisms from the blood Furthermore severe thrombopenic purpura is an unusual complication of this disease There was no evidence that this patient had acute rheumatic fever or any of the other infections listed

Careful consideration must be given to the possibility of some disease of the hematopoietic system Many of these may run a severe acute course with high fever simulating an acute infection The results of the examinations of the peripheral blood and the bone marrow seem to exclude leukemia and aplastic or myelophthisic anemia There was no splenomegaly and there were no associated findings to make one suspect sarcoidosis miliary tuberculosis fulminating liver disease or some rarer entity such as Gaucher s disease

Three major possibilities remain

(1) Essential or primary thrombocytopenic purpura

(2) Purpura as a manifestation of systemic lupus erythematosus

(3) Thrombotic thrombopenic purpura

Idiopathic purpura is rarely accompanied by either a marked febrile reaction or jaundice Both of the other possibilities are infrequent in occurrence Systemic lupus erythematosus may have a very acute onset with high fever and purpura and there may be no joint or cutaneous lesions Thrombotic thrombopenic purpura is a distinctive clinical syndrome the salient features of which are fever

thrombocytopenia a rapidly progressing hemolytic type of anemia and bizarre non localizing cerebral and visceral manifestations Icterus has been reported in over half of the cases and aphasia has frequently been present The illness often ends fatally in one to three weeks The symptoms result chiefly from the obstructive effect of thrombi in small vessels These disturbances usually are most evident in the central nervous system where there is such a close relationship between adequate circulation and normal cellular function Platelet thrombi might account for the numerous abnormalities involving various organ systems in the present case

In view of the close resemblance between the findings in this case and those described in cases of thrombotic thrombopenic purpura this seems the most likely diagnosis

Anatomical Diagnosis (Autopsy No 21696) History of rheumatic fever in childhood with subcutaneous nodules and polyarthritis Chronic rheumatic endocarditis of aortic and mitral valves Aortic insufficiency Hypertrophy of left ventricle Mild mitral insufficiency Recent non bacterial thrombotic vegetations of aortic and mitral valves Multiple recent emboli and platelet thrombi of small vessels throughout the viscera Infarct of posterior wall of left ventricle and numerous tiny fresh myocardial infarcts and scars Severe passive congestion of lungs and liver with acute central liver necroses Multiple small infarcts of spleen kidneys pancreas and brain History of thrombocytopenia and purpura Hemorrhage in bladder mucosa Lupus erythematosus disseminatus periarterial fibrosis of spleen wire loop lesion of renal glomeruli Patchy rheumatic pneumonia Extramedullary blood formation in the spleen Basophilic cytoplasmic granules in liver and adrenal cortex Non-calcified basophilic deposits in and about small vessels in the corpus striatum

This case showed an unusual combination of lesions There was scarring of the aortic valve with evident aortic insufficiency and left ventricular enlargement There was moderate scarring of the mitral valve and chordae tendineae but no auricular endocarditis There were small friable vegetations on both the aortic and mitral valve Histologically these were fresh non bacterial thrombotic vegetations There were evidently numerous tiny emboli in the coronary vessels and elsewhere throughout the body In the myocardium these had produced numerous tiny necroses and fresh scars and there was a large recent infarct of the posterior wall of the left ventricle There were also numerous infarcts in the spleen and kidneys and minute ones in the pancreas and brain There were granular thrombi in the small arteries and arterioles in these organs and elsewhere and the great abundance and minute size of many of these thrombi suggested that some of them may have formed locally in the minute vessels and did not represent emboli This was particularly interesting in view of the fact that the patient had a low platelet count terminally and had numerous petechiae and large cutaneous hemorrhages recalling the rare cases of platelet thromboses with

thrombocytopenia The spleen showed striking periarterial fibrosis and there were also thickened capillary loops in some glomeruli of the kidneys The patchy pneumonia was associated with focal thrombosis of capillaries and necrosis of alveolar walls resembling a rheumatic pneumonia

SUMMARY This 22 year old white man who had a history of chronic rheumatic heart disease developed an acute illness lasting for three weeks and characterized by epigastric pain vomiting drowsiness aphasia con vulsions coma severe anemia thrombopenic purpura high fever leuko cytosis and azotemia The most likely diagnoses seemed to be systemic lupus erythematosus or thrombotic thrombopenic purpura At autopsy there were chronic rheumatic endocarditis of the aortic and mitral valves MULTIPLE RECENT EMBOLI AND PLATELET THROMBI OF SMALL VESSELS throughout the viscera myocardial infarction, LUPUS ERYTHEMATOSUS with periarterial fibrosis of the spleen and wire loop lesions of the glomeruli and patchy rheumatic pneumonitis Thus the patient had widespread lesions of thrombotic thrombopenic purpura as well as chronic rheumatic endocarditis and the splenic lesions characteristic of systemic lupus erythematosus

IV

(#484774 Admitted December 20 1948 Died January 21, 1949)

(*Continued from page 575*)

DISCUSSION This patient had had severe arterial hypertension for several years Excruciating pain involving numerous areas was the predominant feature of the final illness but physical examination and x ray studies of the bones revealed no recognizable basis for the patient s complaints Evidence of weight loss was striking There was a lid lag and the eyes were said to be prominent but this might have been a result of the profound loss of weight The thyroid gland was normal in size Rhonchi were heard over the chest and the breath sounds at the bases were tubular The liver was possibly a little en larged and the prostate was enlarged and firm, but no evidence of neoplasm was detected He had fever from time to time, and there was a variable elevation of the leukocyte count The x ray findings indicated an interlobar effusion but attempts to obtain fluid were unsuccessful

Thus in this case the history physical examination and clinical course which if correctly interpreted usually give clues to the diag nosis were too vague to be of much help It was thought on the ward

that the patient might have lupus erythematosus or some type of pyogenic infection with empyema and a brain abscess or possibly miliary tuberculosis

The basal metabolic rate was elevated The determinations were probably not satisfactory owing to his extreme discomfort and fever In addition elevation of the BMR is not an uncommon finding in patients with severe hypertension When these facts are considered along with the clinical picture it seems highly unlikely that this man had true hyperthyroidism

The only reason for considering the diagnosis of systemic lupus erythematosus is the rather bizarre character of the whole picture It would be difficult to imagine this disease running its entire course without skin joint lymph node renal or hematological changes The pains were not of the type usually associated with the muscle involvement seen in cases of lupus and for what it is worth muscle biopsy did not show the characteristic lesions There were no localizing *signs to suggest a brain abscess If an empyema were the cause* of the pulmonary shadow many attempts to demonstrate this were unsuccessful Blood cultures were never positive Tuberculosis remains as the best possibility among the infections but since there was no positive evidence in its favor this would have to be a diagnosis of exclusion

Two clues stand out which may be related to each other and to the pains One is the swelling which developed along one rib and the other is the elevated blood calcium in the presence of normal serum protein level and normal blood phosphorus The hypercalcemia persisted in the face of a mounting blood nonprotein nitrogen When the kidney fails and phosphorus is retained the blood calcium tends to drop and may reach low levels unless the parathyroids are stimulated to increased activity and a secondary hyperparathyroidism develops Assuming that this man had a genuine *hypercalcemia* what are the conditions which might have caused it?

(1) *Vitamin D intoxication* is one possibility It may be associated with skeletal pains There was no history of excessive intake of vitamin D and the other features of this type of intoxication were not present

(2) True *hyperparathyroidism* seems unlikely The phosphorus was not depressed in the presence of reasonably good renal function The serum phosphatase activity was not elevated and no skeletal changes were seen in the x ray pictures

(3) *Multiple myeloma* is more difficult to exclude since cases have

been described in which there were no visible changes in the bone or abnormal serum protein levels No Bence Jones protein was found in the urine The swelling of the rib would suggest this possibility, but no lesion of the rib was detected by the radiologist

(4) There was no *rapid skeletal rarefaction* to account for the elevated serum calcium although the inactivity resulting from the severe pain might have led to some calcium mobilization

(5) Some cases of *sarcoidosis* have been presented recently in which there were high serum calcium levels In some instances the usual clinical manifestations of this disease were absent, and operation was performed for parathyroid tumor This diagnosis can only be eliminated here by finding a more satisfactory one to supplant it Cases of tuberculosis have been reported in which hypercalcemia was present but proof of the diagnosis of tuberculosis was not recorded These may have been cases of sarcoidosis

(6) In the final category are those cases of *osteolytic metastases* from carcinomas We must also include here certain cases of carcinoma of the breast and lung in which bone pain may be prominent in the absence of x ray or postmortem evidence of skeletal metastasis *in the bones examined*

There was no note of any alteration of the breast and I know of no cases of carcinoma of the breast in males which have been associated with hypercalcemia On the other hand there was an opaque area in the lung field from which fluid could not be obtained on repeated trials I believe that this was a carcinoma of the lung with bone metastases which were not evident in the x rays taken This diagnosis offers an explanation of the prominent pain the loss of weight the fever and possibly the nervous system symptoms which may have been due to metastatic lesions This case brings to mind the old aphorism that one should think of carcinoma when pain in the bones is prominent and nothing can be seen in the x ray to account for it Conceivably the pain might have been due to acute pulmonary hypertrophic osteo arthropathy which may appear early in the course of a pulmonary neoplasm and may simulate an acute polyarthritis On the other hand the development of the rib swelling suggests metastases to bone

ANATOMICAL DIAGNOSIS (Autopsy No 21624) Undifferentiated bronchogenic carcinoma right middle lobe bronchus with metastasis to hilar lymph nodes right 5th rib right lower lobe and liver Fibrous pleural adhesions right

This was an anaplastic carcinoma arising in the right middle lobe bron

chus and extending widely throughout this lobe as solid sheets of infiltrating tumor Much scarring and necrosis were present The lower lobe showed massive lymphatic plugging by tumor cells The tumor had metastasized to a hilar lymph node to the liver and to bone In the absence of much active bone formation it is understandable that the serum phosphatase was only slightly elevated and it is likewise understandable that a bed ridden man who had lost much weight in 3 months and who had what were probably diffuse bony metastases should have an elevation of blood calcium Many cases of tumor metastasizing widely to bone and showing elevated blood calcium with or without high phosphatase levels are to be found in the literature The unusual feature of this case was the negative bone x rays in spite of bony lesions significant enough to cause the chemical alterations However it is possible that the progressive rarefaction of bones resulting from inactivity and cachexia might have accounted for the chemical changes in the absence of tumor metastases

SUMMARY This 45 year old white male with severe hypertension developed pains in numerous skeletal areas accompanied by no objective findings on physical or radiological examination of the bones until late in the illness when a fusiform swelling of one rib was noted There was a circumscribed area of opacity between the middle and lower lobes of the right lung There were evident weight loss intermittent fever leukocytosis and elevation of serum calcium with normal serum albumin and phos phorus The coincidence of bone pain and elevated serum calcium seemed significant Analysis of these and other factors led to the diagnosis of pulmonary carcinoma This diagnosis was confirmed at autopsy The tumor was an anaplastic BRONCHIAL CARCINOMA which had metastasized to lymph nodes bone and liver

V

(MIBH #47677 Admitted December 13 1952
Died January 1 1953)

(*Continued from page 577*)

DISCUSSION Before proceeding to a consideration of the diag nosis I would like to comment on several points in the case history One important physical finding was omitted from the abstract Al most everyone who wrote a note about this patient commented on his excessive sweating This was noted in the initial work up and it was one of the findings which made us consider the possibility of pheochromocytoma One further point you have noted in the ab stract that in the initial urine concentration test the specific gravity

rose to 1 050 The intern made a note opposite the latter figure 'probably in error' In going over the record I found that the test was carried out on the same day as the intravenous pyelography The very concentrated specimen was obtained after the pyelograms I have no doubt therefore, that the figure of 1 050 was correct since Diodrast is excreted in high concentration and may contribute heavily to the specific gravity of the urine This point should always be borne in mind in scheduling the concentration tests

This patient had severe hypertension of the so called malignant or accelerated type These are clinically descriptive terms which have no significance in pathology Malignant hypertension may be caused by a variety of pathological conditions most of which eventuate in some form of renal failure In considering cases of severe hypertension it is best to think first of the remediable causes

(I) REMEDIABLE CAUSES OF SEVERE HYPERTENSION

(A) *Vascular Anomalies* The most important of these is coarctation of the aorta This patient obviously did not have a significan degree of coarctation It is known that he had a normal tension prior to the age of 27 years Furthermore there were strong arterial pulsations in the lower extremities Another type of vascular anomaly is that which causes obstruction to the flow of blood to one or both kidneys for example partial occlusion of the renal artery or complete occlusion of a branch of the renal artery There was nothing in the pyelograms in this case to suggest such an anomaly but in the absence of angiography such an anomaly cannot be excluded

(B) *Endocrine Disease* The most important remediable endocrine diseases causing hypertension are those associated with the adrenal glands This patient did not have the stigmata of a cortical adrenal tumor On the other hand pheochromocytoma was a possibility which was given very serious consideration The points *in favor* of a pheochromocytoma were (1) the age of onset of the hypertension (2) the suddenness of onset of the hypertension (3) excessive sweating, and (4) a firm mass in the region of the left kidney noted in the initial physical examination in another hospital As I have said the excessive sweating was commented upon frequently in the clinical record The sweating was more than the moisture of the palms which one sees in various types of nervous tension It involved the face the upper part of the chest, and during the physical examinations perspiration frequently dripped from the axillas This was one of the symptoms which originally led us to carry out tests designed to ex

clude a pheochromocytoma Relative to the firm mass in the region of the left kidney I cannot attach much significance to this observation because we never observed such a tumor here On the other hand there are six points *against* pheochromocytoma (1) The sustained non paroxysmal type of hypertension Never during the long period of observation did this patient s blood pressure approach normal The lowest diastolic pressure recorded was 110 However paroxysmal hypertension in cases of pheochromocytoma is far less frequent than was originally supposed Since the introduction of the new adrenolytic drugs the diagnosis of pheochromocytoma is being made in an increasing number of cases of sustained hypertension and it would appear from recent figures that about half of the cases have sustained hypertension (2) The absence of any disturbance in the carbohydrate metabolism This patient s fasting blood sugar was actually low rather than high Disturbances in carbohydrate metabolism are usually associated with the paroxysmal type of hypertension and they are frequently absent when the hypertension is of the sustained type The recent work of Goldenberg and his associates has thrown new light on this subject By analyzing the catechol content of pheochromocytomas they have found that the pressor agent in many of the tumors is made up largely of norepinephrine rather than epinephrine Norepinephrine does not have the marked effect on carbohydrate metabolism that is exhibited by epinephrine In fact norepinephrine may produce a type of hypertension which closely simulates that of essential hypertension (3) The absence of any elevation in the basal metabolic rate This patient s basal metabolic rate was plus 9 in this hospital and it was plus 1 in the other hospital Here again however disturbances in the metabolic rate occur chiefly in the paroxysmal form of hypertension (4) The absence of a fall in blood pressure in the piperoxan test I am afraid that we may have attached too much significance to a single negative response It is now well known although it was not so well known when the test was performed on this patient that the piperoxan test may be negative in a certain number of these patients particularly in those with sustained hypertension during periods when the norepinephrine or epinephrine content of the blood is not excessive (5) The absence of any significant displacement of the kidneys in the pyelograms This is not decisive since the tumor is not always of sufficient size either to displace the kidney or to deform its pelvis (6) The lack of any palpable tumor either in the physical examination or by direct palpation of the adrenals and kidneys at the time of the sympathec

tomies This again is not decisive, for pheochromocytomas may arise in chromaffin tissue located elsewhere for example in the organ of Zuckerkandl which is located near the bifurcation of the aorta In fact, pheochromocytomas have been found in a number of areas, including the thorax

(C) *Unilateral Disease of the Kidney* It is well known that unilateral kidney disease of various types may produce the picture of malignant hypertension However almost all of these types of disease are discoverable in pyelograms The commonest is unilateral pyelonephritis Less common are unilateral infarction renal tumors and tuberculosis All of these diseases, with the possible exception of infarction should have been apparent in the pyelograms Not only did this patient have normal pyelograms but as far as one could tell the Diodrast was excreted in excellent concentration by both kidneys even as late as 18 months after the onset of the hypertension I do not believe that this patient had unilateral kidney disease, although one cannot exclude occlusive disease of the renal arteries or renal infarction

(II) NON REMEDIABLE CAUSES OF SEVERE HYPERTENSION

Non remediable causes of severe hypertension are almost always attributable to bilateral renal disease Under this heading one has to consider congenital polycystic disease chronic glomerulonephritis, and chronic pyelonephritis If the patient had had any of these types of disease it should have been apparent when he first came under observation that there was some primary disturbance in the kidneys Polycystic disease does not usually cause severe hypertension until the renal function has become considerably reduced The same may be said of chronic glomerulonephritis and chronic pyelonephritis The absence of albuminuria in the early phases of the illness is also a strong point against primary renal disease Under this heading one must also consider the rarer diseases such as systemic lupus and periarteritis nodosa This patient had none of the well known collateral manifestations of these diseases If the patient had bilateral renal disease and I am sure that he *did* have at least terminally then it was most likely of the arteriolosclerotic type By this I mean the so called nephrosclerosis which is found in patients who die of renal failure after a prolonged period of severe hypertensive disease There is considerable question in such cases whether the renal disease is the cause or the result of the hypertension In either event it is the factor which frequently leads to death

On the basis of statistical considerations and in the absence of information clearly indicating another type of disease I am driven to the conclusion that the patient had so called essential hypertension of the malignant type with arteriolosclerotic nephritis However I feel very insecure in making this diagnosis and I must make it clear again that pheochromocytoma has not been satisfactorily excluded

There are certain other details which we must comment on (1) The heart failure I believe this was due to hypertensive disease and that the patient will be found to have the usual hypertrophy and dilatation of the heart Here again it should be pointed out that heart failure coming on in the absence of renal failure is uncommon in the usual type of severe hypertension in young individuals However heart failure may be a relatively early and striking manifestation in cases of persistent hypertension due to pheochromocytoma I am impressed by the fact that the patient already had striking electrocardiographic evidences of cardiac abnormalities when he first came under observation These consisted chiefly of widening of the QRS T angle with evidences of left ventricular hypertrophy (2) The condition of the lungs Certainly this patient had pulmonary congestion of a relatively marked degree probably due to left ventricular failure In addition to this it seems likely that he had either pneumonia or pulmonary infarction in the last phase of his illness (3) The pericardial friction rub This was probably due to a uremic pericarditis Such friction rubs in cases of severe hypertension should always arouse the suspicion of dissecting aneurysm of the aorta However there were no other evidences of dissecting aneurysm and I do not believe that one was present in this case

ANATOMICAL DIAGNOSIS (*Autopsy MIBH No A 53 1*) *Scars of bilateral thoraco lumbar sympathectomy posteriorly* Pheochromocytoma retroperitoneal Passive congestion of lungs Edema pulmonary bilateral Pulmonary hemorrhage focal old and fresh Hydrothorax bilateral Cardiac hypertrophy Uremic pericarditis with effusion Arteriolar sclerosis generalized Passive congestion of small intestine Passive congestion of liver Pancreatic arteriolar sclerosis marked Arteriolar nephrosclerosis with thrombosis Infarct of kidney left Edema cerebral

The autopsy disclosed the changes associated with advanced arteriolar sclerosis The heart was markedly enlarged weighing 580 grams and there was evidence of so-called uremic pericarditis with a pericardial effusion of some 300 ml The lungs were congested and there was bilateral pulmonary edema Focal hemorrhages had taken place Proliferative sclerosis of the small arterioles was most conspicuous in the kidneys but was also encountered elsewhere particularly in the pancreas and in the periadrenal adipose tissue Necrotizing changes of these vessels were not encountered The

kidneys also showed moderate numbers of scarred glomeruli and atrophic tubules There was a small fresh infarct in the left kidney The brain was diffusely edematous but there were no focal areas of hemorrhage or degeneration

The striking finding was a small well encapsulated tumor at the lower pole of the right kidney bulging medially outside the renal pelvis but apparently within a reflection of the renal capsule This tumor was 2 5 cm in diameter It was soft and red brown in color owing to its high vascularity Microscopically this proved to be a pheochromocytoma identified by its morphology and by its characteristic staining reaction

In retrospect it seems quite probable that the pheochromocytoma was functional and initiated and maintained the severe hypertension from which this patient suffered The arteriolar changes were doubtless secondary to prolonged hypertension The tumor was of such small size and unusual location as to escape demonstration by intravenous or retrograde pyelography or conventional exploration at the time of sympathectomy A search of the literature discloses only two or possibly three tumors of this nature in a comparable location

SUMMARY This 29 year old man had had periodic occipital headaches since 1940 and nocturia since 1946 He served in the Army during World War II and was believed to have normal blood pressure and normal urine when discharged in 1946 His blood pressure was 124/78 in July 1950 When admitted to hospital in January 1951 he had persistent and severe hypertension markedly thickened peripheral arteries and extreme narrowing and beading of the retinal arteries Pyelograms were normal and gross renal function was within normal limits The blood pressure did not fall during a piperoxan test Direct palpation of the adrenals and kidneys at the time of lumbodorsal sympathectomy disclosed no tumor or other abnormality During a two year period of close observation the diastolic pressure never fell below 110 in spite of the sympathectomy and the use of several potent drugs both singly and in combination There were episodes of acute pulmonary edema and finally rapidly progressive renal failure with the general picture of terminal malignant hypertension After discussing the causes of severe hypertension the conclusion was reached that the patient had arteriolar nephrosclerosis of the malignant type At autopsy the diagnosis of arteriolar nephrosclerosis was confirmed but there was in addition a small PHEOCHROMOCYTOMA imbedded in the lower pole of the right kidney It was believed that the hypertension was due to the tumor and that the cardiovascular renal changes were due to the hypertension

VI

(MIBH #46761 Admitted February 9 1951
Died February 26 1951)

(*Continued from page 580*)

DISCUSSION There can be no question about the fact that this patient had scleroderma of the diffuse type The physical manifestations of the disease were all quite characteristic The distribution and appearance of the skin lesions was typical with involvement chiefly of the hands and feet the face the base of the neck and the upper chest Everyone commented upon the mask like facial expression and the difficulty which the patient experienced in opening her mouth The Raynaud phenomena in the fingers and toes are such regular manifestations of the diffuse type of scleroderma that they require no comment The x ray appearance of the esophagus was such as to lead the roentgenologist to come to an independent opinion that the patient had scleroderma The history of arthritis of the type manifested by this patient is also frequently encountered in scleroderma For some reason which is not at present understood patients with scleroderma also frequently give a history of having been told that they had hyperthyroidism and a number of them like this patient have been subjected to thyroidectomy On the other hand the history of edema is rather unusual Many patients with diffuse scleroderma exhibit some degree of subcutaneous edema but the edema which this patient had five years before and again one year before coming to the hospital was of a different type The edema of scleroderma is not usually dependent It does not involve the peritoneal cavity and it does not respond to diuretics

In addition to the clinical findings we have in this patient histological confirmation of the diagnosis of scleroderma

Since this patient unquestionably had scleroderma the remainder of the discussion must be centered around the question Can all the findings be accounted for by scleroderma?

Scleroderma is a disease which affects primarily collagenous tissue Since this type of tissue is widely spread through the body almost all organs and tissues may be involved In some cases only a few organs may be affected and the disease has a tendency to be spotty in distribution There may be extensive involvement of the intestines liver spleen and skeletal muscles The involvement of the arteries

may be widespread In the kidneys the vascular changes may be of an inflammatory type suggesting an acute arteritis Alterations in kidney function are rarely severe Albuminuria may occur late in the disease but there is almost never any nitrogen retention The elevation in blood pressure which may appear in the pre terminal phase is probably attributable to the renal lesion Involvement of the heart may be quite extensive The heart becomes enlarged Histologically there is a fibrous myocarditis which is attributed to a reduction in coronary blood flow caused by the changes in the arteries Clinically in addition to the enlargement of the heart there may be myocardial insufficiency and the electrocardiogram may show evidence of myocardial damage The Q T interval is prolonged in some cases The lungs may show extensive fibrosis Involvement of the glands of internal secretion has been commented upon frequently Thyroid disease has been suspected in a number of cases There may be alterations in the basal metabolic rate The pigmentation of the skin which occurs in some cases has been attributed to involvement of the adrenals The fasting blood sugar is frequently low

In consequence of what has just been said it is clear that most of the findings in this case could be explained on the basis of scleroderma There are two aspects of the problem however which require further discussion the cerebral symptoms were very conspicuous features of the terminal illness The patient had a long history of severe headache associated with tinnitus and sometimes accompanied by nausea and vomiting These symptoms were increased terminally and were accompanied by convulsions papilledema at least one exudate in the optic fundi cervical rigidity, and an increased cerebrospinal fluid pressure The following explanations of these symptoms have to be considered

(1) *Brain Tumor* One wonders about the tumor which was removed from the roof of the patient s mouth in 1949 This tumor is said to have been present for 20 years and the patient was told that it was a benign bone tumor There was no local recurrence and I believe that this tumor was of no significance There were no localizing signs of a brain tumor, but under these circumstances we occasionally find unsuspected tumors of the frontal lobes

(2) *Intracranial Aneurysm* A long history of headaches is sometimes encountered in cases of intracranial aneurysm The occurrence of crenated red blood cells in the spinal fluid brings this diagnosis to mind However I cannot conceive that a cerebral aneurysm produced

all the symptoms in this case and there were none of the localizing signs associated with an aneurysm

(3) *Cerebral Hemorrhage or Thrombosis* These might have occurred secondarily but I do not believe that either was the primary cause of the cerebral symptoms

(4) *Encephalopathy* I refer here to the type of picture which is seen in cases of severe hypertension This is attributable to cerebral edema and is sometimes associated with extensive vascular disease of the brain and multiple small hemorrhages In view of the rapid increase in the diastolic pressure and the increased cerebrospinal fluid pressure and papilledema it appears to me that this is the most likely explanation of the cerebral symptoms I have not found a description of such symptoms in cases of scleroderma but I believe that the picture is consistent with the renal and vascular changes which occur in scleroderma

The other condition which deserves special consideration is that of the heart As I have said myocarditis cardiac enlargement and myocardial insufficiency of the type shown by the patient have been described in cases of scleroderma One must review in one s mind all the other causes of myocardial failure but in this instance the ones which deserve particular consideration are the following (1) *Cardiac failure associated with valvular disease* The history of edema five years before admission to the hospital suggests some prior cardiac disease The murmurs were consistent with a mitral lesion and it is possible that the patient had a chronic rheumatic mitral valvulitis There was little in the final illness to support such a view but I do not believe that an old mitral lesion can be satisfactorily excluded (2) *Cardiac failure associated with pericarditis* Sudden enlargement of the heart should always raise a question of pericardial effusion In the fluoroscopic examination the heart appeared to show a normal type of movement and a precordial impulse was visible There were none of the evidences of cardiac tamponade (3) *Failure due to myocardial disease* Such disease may have been of the type usually associated with scleroderma and I think that that is the best explanation of the findings in this case The rapid increase in the size of the heart and the electrocardiographic changes are consistent with myocardial disease If the patient had a mitral lesion one would also have to give serious consideration to rheumatic myocarditis I think however that this is unlikely

There remains one further matter to consider namely the role of

adrenocorticotropic hormone and cortisone in the production of this patient s symptoms Edema elevated blood pressure and heart failure may be caused by these agents There are however, several strong points against this possibility The dosage of the agents was rather small When symptoms occur after adrenocorticotropic hormone and cortisone they usually come on early rather than late in the course of treatment In this case the symptoms came on late and continued to grow worse after the drug had been discontinued Furthermore no abnormalities were noted in the studies of the serum electrolytes If adrenocorticotropic hormone and cortisone accounted for any part of the patient s symptoms it was probably in the form of temporary amelioration followed by exacerbation after the agents had been discontinued However even this seems unlikely since the symptoms appear to have been steadily progressive without relation to the two drugs The temporary improvement in the skin was an exception to this generalization

We have still to explain the terminal fever and leukocytosis I believe that these may be attributed to pneumonia The abdominal distention and blood in the stools also require explanation There may be extensive involvement of the intestines in scleroderma and I believe that the abdominal symptoms can best be explained on the basis of infarction or ulceration of the type seen in cases of malignant hypertension The jaundice may have been due to congestion of the liver plus anoxia resulting from pulmonary fibrosis and pneumonia

I would prefer to explain everything in this case on the basis of diffuse scleroderma but I should not be surprised to find a more widespread and more intense vascular disease than one usually encounters in scleroderma In addition there may also have been an old rheumatic deformity of the mitral valve The terminal fever and jaundice are probably attributable to bilateral bronchopneumonia

ANATOMICAL DIAGNOSIS (Autopsy MIBH No A 51 13) Scleroderma generalized progressive Tracheitis acute Bronchiolitis acute focal Fibrosis pulmonary focal interstitial Hydrothorax bilateral Cardiac hypertrophy Rheumatic valvulitis inactive with scarring of mitral valve slight Arteriolar sclerosis generalized atypical Esophagitis acute Focal necrosis of liver pancreas and adrenal cortex Arteriolar nephrosclerosis atypical marked Cyst of pituitary gland pars anterior Focal hemorrhages into occipital leptomeninges Cerebral edema focal

Changes were encountered in most if not all of the tissues examined The diversity of these changes is indicated by the numerous anatomical diagnoses recorded Some of the changes have been previously described

in patients dying of generalized scleroderma These include the peculiar patchy fibrosis in the lungs generalized involvement of arterioles with obliterative proliferation of endothelium and intimal cells and renal damage probably secondary to this atypical arteriolar sclerosis Acute esophagitis was unsuspected in this patient and may possibly be related to the not uncommon involvement of the esophagus in scleroderma Focal areas of necrosis in the liver pancreas and adrenal cortex were conspicuous microscopically It is possible that insofar as pancreas and adrenal cortex are concerned focal areas of marked ischemia could have been produced by the striking arteriolar changes

Certain of the cerebral symptoms which became evident in the terminal stages of the disease are possibly to be explained on the basis of focal cerebral edema There was sclerosis of the cerebral arterioles No necrotizing changes were present Focal areas of hemorrhage were encountered in the leptomeninges The heart was enlarged weighing 430 grams It is possible that some of the enlargement was attributable to slight diffuse interstitial edema but there was also evidence of thickening and fibrosis of the mitral valve and its chordae tendineae suggesting a healed inactive rheumatic process although the distortion of the valve opening was indeed minimal It is quite possible that the focal cerebral edema hyperemia and perhaps even the leptomeningeal hemorrhages were the result of hypertensive encephalopathy secondary to the generalized and renal vascular disease

The arteriolar changes described above differed somewhat from those seen in classic arteriolar nephrosclerosis with hypertension The walls particularly the intimal portions of these blood vessels were more cellular than one usually finds in the hypertensive state alone

SUMMARY A housewife 52 years of age had headaches for many years In 1946 she developed transitory dependent edema Early in 1949 many of her joints became painful and stiff and there were episodes of numbness tingling and blanching of the fingers and toes In February 1950 she again became edematous for a period of two months When admitted to the hospital in October 1950 there was obvious scleroderma involving the extremities face neck and chest Many joints were stiff and painful on motion The heart was enlarged and there was an apical systolic murmur Under treatment with adrenocorticotropic hormone and cortisone the condition of the skin and joints improved but the headaches became more severe and were accompanied by nausea the blood pressure rose the heart increased in size and there were evidences of myocardial insufficiency After medication had been discontinued her condition rapidly grew worse with convulsions papilledema albuminuria tarry stools congestive failure jaundice high fever and death in coma In discussing this complex problem it was pointed out that virtually all of the findings could be accounted for by diffuse scleroderma with widespread visceral involvement although it was believed that there might also be a chronic rheumatic deformity of the mitral valve and a terminal pneumonia Autopsy disclosed an unusually intense and widespread vascular disease of the type associated with DIFFUSE SCLERODERMA There was an old rheumatic mitral valvulitis

VII

(#111687 Admitted April 27, 1951 Died April 29 1951)

(*Continued from page 582*)

DISCUSSION Before one can assemble the diagnostic possibilities the various physiological disturbances must be carefully analyzed and interpreted The first question is whether the dyspnea and cyanosis were due primarily to pulmonary or to cardiac insufficiency It would appear altogether likely that they were primarily due to pulmonary disease At the time of admission when the patient was dyspneic and noticeably cyanotic the lungs were clear of adventitious sounds while the x ray pictures showed extensive changes The heart was not strikingly enlarged the liver was not enlarged, the venous pressure was normal and the circulation time was not significantly prolonged It would seem safe to conclude that the extensive changes in the lungs on roentgen examination should not be attributed to cardiac insufficiency If he had rapidly progressive changes in his lungs I believe that the type of pain which he experienced on exertion might have been the result of increased respiratory effort There was no striking polycythemia no evidence of right sided heart failure and no right axis deviation in the electrocardiogram to attract one to the diagnosis of chronic cor pulmonale

Having concluded that the dyspnea and cyanosis were pulmonary in origin we may now ask about the significance of the marked clubbing of the fingers which had been noted many years before death In 1931 when the clubbing was first noted a diagnosis of emphysema was made but from then until the final illness there was no history of pulmonary difficulty The x ray in 1949 showed evidence of emphysema but no lesion which might account for the clubbing There was no suggestion of any extensive tuberculous infection However, there are two important abnormalities which might have been present although not recognizable in a plain chest film bronchiectasis and congenital cystic disease It is also possible that the clubbing of the fingers was a familial characteristic and not indicative of any pulmonary or cardiac abnormality

Certain other points about the course of the illness are important There was no history of any tendency to repeated respiratory infections Dyspnea on exertion was first noticed only a few months before death it progressed rapidly during the two weeks before admission

although there were no complaints suggesting an acute infection during this period

The diagnostic possibilities seem to fall into several distinct groups

(1) Some acute infection unrelated to any underlying chronic lung disease
 (a) Virus pneumonia
 (b) Fulminating fungus infection
 (c) Activation and rapid spread of an old tuberculous infection
(2) Acute infection complicating an underlying pulmonary disease such as
 (a) Bronchiectasis
 (b) Congenital cystic disease
(3) Acute interstitial fibrosis of the lungs
(4) Neoplastic disease with lymphogenous spread
 (a) Lymphoma
 (b) Carcinoma of the prostate
 (c) Carcinoma of the stomach
 (d) Carcinoma of the lung

Virus pneumonia seems unlikely from the course of the illness and from the extent of the lung changes in the absence of evidences of a severe infection With an infection one does not expect to get such a high leukocyte count with so little fever On the other hand the paucity of physical signs in the presence of extensive x ray changes is compatible with an infection Fungus disease with such a fulminating course seems a remote possibility

In a man of 67 with no previous history of recurrent pulmonary infections one would not expect to find an underlying chronic cystic disease or bronchiectasis The failure of any improvement with penicillin therapy is also evidence against these diagnoses since only streptococci and pneumococci were cultured from the sputum

Extensive tuberculosis may develop in aged individuals without any systemic reaction other than progressive weight loss and a very low grade fever Invasion of the pericardium may occur and when the auricles are involved auricular fibrillation may develop This condition is sometimes mistaken for arteriosclerotic heart disease or neoplasm This man might have had a low grade tuberculous pericarditis complicated by a bronchogenic spread of the tuberculosis two weeks before admission I believe on weighing the various facts that other possibilities are more likely Before leaving the question of tuberculosis however the low sodium and chloride concentrations

in the serum the low arterial blood pressure and the low venous pressure need some consideration in relation to the possibility of Addison s disease It is rather remarkable, particularly in a man of this age that such a degree of sodium depletion should occur without more effect on renal function Significant reductions in serum sodium are usually accompanied by circulatory abnormalities The syndrome of salt depletion shock occurs in many conditions other than Addison s disease The eosinophil count of 11 is against Addison s disease severe enough to produce the electrolyte changes

The rapid development of dyspnea and cyanosis with diffuse pulmonary changes suggests the type of interstitial pulmonary fibrosis described by Rich and Hamman and first discussed by them in several cases presented at these conferences The course is perhaps a little short and the absence of evidence of hypertension in the pulmonary circulation is against this diagnosis These patients however may complain of chest pain may have little fever and may develop leukocytosis late in the disease

Finally the course of this illness the extensive pulmonary shadows the leukocytosis without much fever and the loss of weight suggest a neoplastic disease of the lung spread via the lymphatic system In this type of disease one sees extensive x ray changes with minimal physical findings The gastrointestinal complaints which were stressed by the patient after his admission may furnish a valuable clue Carcinoma of the stomach is known to produce this type of metastatic spread in the lungs The same is true of carcinoma of the prostate and lymphoma The pericardium might have been involved by direct extension of a carcinoma of the stomach into the mediastinum In carcinoma of the stomach with achlorhydria sodium chloride and not hydrochloric acid would be lost in the vomitus This might provide an additional explanation of the sodium deficit

My conclusion is that the patient had carcinoma of the stomach with lymphogenous spread in the lungs

ANATOMICAL DIAGNOSIS (Autopsy No 22999) Acute diffuse interstitial fibrosis of the lungs with hyaline membrane formation pulmonary arteriosclerosis bronchial epithelial metaplasia Squamous carcinoma of the lung with metastasis to regional nodes Non bacterial vegetation of the mitral valve Thrombi pancreas lungs heart and liver Focal myocardial necroses Fibrinous pericarditis Chronic prostatitis Chronic cholecystitis

Both pleural cavities contained a liter of clear yellow fluid and the pericardial cavity contained about 200 ml There was a fine fibrinous pericarditis covering the entire surface of the heart The cut surface of lung

was firm dark red and studded with numerous small dilated alveoli The lungs appeared to be diffusely consolidated

Microscopic sections showed a classic picture of diffuse interstitial pulmonary fibrosis Large fibroblasts occasional mononuclear cells and abundant early collagen formation which caused marked thickening of the walls of the alveoli were noted throughout all sections Hyaline membranes which appeared to be of recent origin lined many of the alveoli Occasionally organizing intra alveolar exudate was present but the widespread change was in the interstitial tissues A poorly differentiated squamous carcinoma of the bronchus was found This was small and had metastasized only to regional lymph nodes

SUMMARY This 67 year old man who had had emphysema and clubbing of the fingers for many years developed dyspnea on exertion cyanosis loss of weight gastrointestinal symptoms and substernal pain The illness progressed rapidly during the two weeks before admission The dyspnea and cyanosis were accompanied by few physical findings but x ray pictures showed progressive changes in both lungs The symptoms were believed to be due to pulmonary rather than cardiac disease since the venous pressure and circulation time were normal and the liver was not enlarged The rapid progress of the dyspnea and cyanosis and the bilateral pulmonary shadows suggested acute interstitial pulmonary fibrosis The extensive lung changes the leukocytosis with only slight fever and the minimal objective findings on physical examination were compatible with the lymphogenous spread of a neoplasm The latter was considered to be the preferable diagnosis Autopsy revealed extensive ACUTE DIFFUSE INTERSTITIAL FIBROSIS of the lungs and a small squamous carcinoma of the lung with metastasis to regional nodes The important lesion was the interstitial fibrosis which undoubtedly accounted for the major symptoms

VIII

(#290930 Admitted May 10 1943 Died May 12 1943)

(*Continued from page 583*)

DISCUSSION There are many possible causes of exsanguinating hemorrhage from the gastrointestinal tract In this case all of the blood was vomited which suggests strongly that the lesion was in the esophagus stomach or duodenum

The story of tarry stools in the past cannot be relied upon The character of the pain its radiation and its relation to eating may be helpful in locating the position of the lesion in the gastrointestinal tract

With *deep penetration of peptic ulcers* the pain shifts to the sides and back there is less tendency toward intermittency of symptoms less relief from food or alkalis, earlier onset after meals and more distress at night Abdominal tenderness becomes evident and persistent soreness develops over the approximate area of pain Posterior radiation of the pain suggests posterior penetration

In lesions of the lower esophagus the pain may be referred laterally but it is usually referred upward even to the neck when the endings of the phrenic nerve in the diaphragm are irritated

In perforating gastric ulcers the pain is usually referred to the left occasionally it is referred to the right when the perforation involves the pancreas

In duodenal ulcers with penetration the level of referred pain is similar to that observed in this patient and reference is usually to the right

It would be very helpful to know the exact time after eating at which exacerbation of the pain occurred Pain immediately after eating suggests a lesion of the cardiac region or lower esophagus pain coming on later points to a lesion in the lower stomach or duodenum One can say no more than that the lesion in this case was probably posterior and relatively high in the gastrointestinal tract

Of the many causes of hemorrhage from the upper intestinal tract we shall consider now only the probable causes of massive hemorrhage in a middle aged woman with syphilis The history of recurrent melena for 5 years although questionable immediately suggests a peptic ulcer Small hemorrhages may be the only symptom before penetration of surrounding structures occurs The pain as described is compatible with a posterior penetrating ulcer Duodenal ulceration invading the pancreas is most likely to bleed profusely but the exacerbation of pain with eating suggests a lesion in the cardiac end of the stomach or lower esophagus

Cirrhosis of the liver with bleeding from an esophageal varix is a common cause of fatal hematemesis but usually pain is not a prominent feature There were no other findings pointing to disease of the liver

Carcinoma of the stomach does not ordinarily give rise to such profuse hemorrhage Carcinoma of the lower esophagus would be expected to produce some dysphagia Furthermore the radiation of the pain was unlike that seen with lesions of this area It is conceivable that there was a carcinoma of the transverse colon with hemorrhage following attachment to and invasion of the stomach

So called splenic anemia and thrombosis of the portal vein are rare causes of hematemesis but there were no findings to suggest their presence here The same may be said for the various blood dys crasias which may be accompanied by gastrointestinal bleeding

There are several syphilitic lesions which may be associated with severe bleeding into the intestinal tract

(1) Gumma of the esophagus This is open to the same objection as carcinoma of the esophagus

(2) Syphilis of the stomach which rarely causes such severe bleed ing would probably have been recognized by the surgeons at operation

(3) Annular ulcerations of the bowel may occur which often bleed profusely However in the one case which I have encountered per sonally the ulcers were present in the jejunum and ileum and there was bleeding from the rectum

(4) Syphilitic aneurysms may become attached to the wall of the esophagus or at other levels of the intestinal tract and finally per forate with fatal hemorrhage The severity of the pain suggests such a possibility in this case This would not account for the history of melena over a five year period

There are numerous other causes of massive hemorrhage which need not be discussed in detail such as foreign body gallstones with duodenal ulceration duodenal diverticula Meckel s diverticulum lymphoma of the gastrointestinal tract benign gastric neoplasms

The persistence of pain and the severity of the bleeding with fatal outcome suggest most strongly

(1) Duodenal ulcer penetrating to the pancreas

(2) Perforation of a syphilitic aneurysm of the aorta

The first is common and the latter rare The history of melena for five years also persuades me to make a final diagnosis of posterior duodenal ulcer with erosion of a pancreatic artery

ANATOMICAL DIAGNOSIS (Autopsy No 18365) Syphilitic aortitis Saccular aneurysm of aorta with rupture into esophagus and exsanguinat ing hemorrhage Recent surgical wounds of upper midline of abdomen and of stomach with ligation of terminal gastric arteries Pulmonary edema Teratoma of left ovary Calcified primary tuberculous complex of left lung Adenoma of thyroid Chromophobe adenoma of hypophysis

The aortic cusps were slightly thickened There was a typical syphilitic aortitis which began at the root of the aorta In the ascending arch there were lipoid deposits along with the syphilitic thickening The transverse and descending aorta showed even more marked intimal thickening and wrinkling In the first part of the descending aorta the syphilitic lesion was

more localized in an area on the posterior wall and the process ended abruptly at the level of the fifth intercostal arteries The mouth of the aneurysm was at the junction of the transverse and descending aorta and measured 2 5 cm in diameter The sac projected upward and a little back ward and measured about 4 cm by 3 cm In its posterior projection the aneurysm had fused with the esophagus and had perforated into it The opening into the esophagus measured 3 5 by 1 5 cm The aneurysmal sac was filled with thrombus material

SUMMARY This 43 year old Negro woman who had occasional melena over a period of five years developed one week before death a dull epigas tric pain which radiated posteriorly and was aggravated by ingestion of food She had massive gastrointestinal bleeding and at operation no bleed ing point was discovered The serologic test for syphilis was positive The severity and persistence of the pain and the severe and continued bleeding suggested either a posterior duodenal ulcer with perforation into the pancreas or a syphilitic aneurysm with rupture into the gastrointestinal tract The first of these possibilities was considered the more likely because of its relative frequency and because of the five year history of melena Autopsy revealed a SYPHILITIC ANEURYSM OF THE AORTA WHICH HAD PERFORATED INTO THE ESOPHAGUS

IX

(#430844 Admitted October 9 1947 Died October 21 1947)

(*Continued from page 585*)

DISCUSSION There are two major problems in this case (1) the nature of the cardiac disease and (2) the precipitating cause of the cardiac insufficiency

The enlargement of the right side of the heart and the prominence of the pulmonic conus suggest that there was hypertension in the pulmonary circuit There were significant cardiac murmurs and the physical signs plus the large notched P waves and the evidence of pulmonary hypertension suggest that there was mitral stenosis There were changes over the base of the heart which also lead one to believe that there was organic disease of either the aortic or the pulmonic valve—a difficult decision here in the absence of any peripheral signs of aortic insufficiency Despite the history of a cardiac condition before the age of 6 years it seems reasonable to conclude that this woman had rheumatic heart disease The shape of the heart suggests

also that there may have been in addition to the valvular involvement some pericardial disease

The patient had complained of a minimal degree of exertional dyspnea for many years but full blown symptoms and signs of cardiac insufficiency appeared abruptly 2 months before death At the same time she began to have pains in the substernal region and left chest made worse by exercise The various pathologic processes which constitute the underlying causes of cardiac disease are frequently of a progressive nature and may in time produce cardiac failure regardless of therapy However the rate of progression of the underlying disease may be slow and in many cases *congestive failure* does not supervene until it is precipitated by some added factor Many of the *precipitating factors* can be prevented or successfully treated Their recognition is therefore of great practical importance

Infection is perhaps the most important of the precipitating factors A simple upper respiratory infection may be sufficient to upset the balance In the present case however we have to consider more serious factors such as pneumonia or an acute exacerbation of rheumatic fever or bacterial endocarditis Pneumonia may have complicated the failure but there was nothing to suggest that it was an initiating factor in the terminal illness

Unusual exertion another important precipitating factor was apparently not involved The patient s cough when coupled with the pain in the chest makes one suspect that the significant factor was pulmonary embolism This possibility is further strengthened by the patient s sudden death while on the bedpan

Active rheumatic myocarditis might itself have been the precipitating factor Except for the fever there was during the terminal illness none of the other manifestations of active rheumatic disease such as arthritis *No predisposing upper respiratory infection* had occurred before the onset Furthermore there was no conduction defect in the electrocardiogram and no gallop rhythm was mentioned

Certain features of the illness suggested bacterial endocarditis The illness began with anorexia and loss of weight and there was a history of fever and sweats The spleen was enlarged but no clubbing of the digits or petechiae were noted *Multiple emboli to the lungs* were suggested by the clinical course the chest pain and the increased bilirubin content of the blood Emboli might have come from the periphery or from mural thrombi The marked degree of dyspnea without apparent pulmonary edema suggests the presence of multiple

small pulmonary infarcts of the type seen with vegetative endocarditis The soft diastolic murmur heard in the 3rd left interspace without the accompanying peripheral signs of aortic insufficiency might be indicative of pulmonic insufficiency If this patient had bacterial endocarditis on the pulmonic valve multiple pulmonary emboli would be explained and the absence of petechiae would be accounted for

The so called malar flush and the brownish pigmentation of the skin suggest the possibility of lupus erythematosus but there is little else to support this diagnosis

My final diagnosis is chronic rheumatic heart disease with aortic and mitral valve disease multiple pulmonary emboli possibly secondary to bacterial endocarditis with vegetations in the right side of the heart

ANATOMICAL DIAGNOSIS (Autopsy No 20870) Calcific aortic mitral and tricuspid stenosis Cardiac hypertrophy and dilatation Myocardial scarring Organizing mural thrombus right auricular appendage Emboli in pulmonary and splenic arteries Multiple infarcts of lungs Pulmonary edema Atelectasis Infarcts of spleen splenomegaly Chronic passive congestion of liver with cardiac cirrhosis Hydrothorax and hydropericardium Extramedullary blood formation spleen Osteoma of rib Ulcerative esophagitis Tuberculosis of bronchial lymph nodes and spleen

The heart was enlarged and dilated The mitral valve was shortened and thickened and its cusps were fused The chordae tendineae were shortened and thickened There was a real fish mouth stenosis The aortic valve showed fusion and thickening of its cusps At the line of fusion of two of the cusps there was a calcified ring in the center of which was a small opening measuring 5 mm in width through which the blood had been forced At the apex of the left ventricle the wall was thinned out and on section showed grayish white scar tissue on which there was a mural thrombus The tricuspid valve showed fusion of its cusps with shortened and thickened chordae tendineae so that the ostium of the valve had been narrowed to a thin slit like opening measuring 2 cm in length The right atrium was tremendously dilated and a thrombus was present The mouth of the right coronary artery was appreciably narrowed by arteriosclerotic plaques In both lower lobes there were infarcts which measured 3 to 4 cm in diameter The liver was enlarged and showed an irregularly lobulated surface The spleen was enlarged and there was an infarct 2 cm in diameter beneath the capsule There was also an infarct 2 cm in diameter in the left kidney

In view of the history of rheumatic fever this disease was probably responsible for the great calcific distortion and stenosis of the valves The myocardial scarring was not confined to a perivascular distribution but was diffuse

SUMMARY This 34 year old woman who had had chronic endocardial

disease since early childhood developed increased dyspnea cough and episodes of chest pain suggestive of multiple pulmonary emboli Examination revealed cardiac enlargement with signs of mitral and aortic valve disease splenomegaly and mild icterus with leukocytosis She died suddenly while on the bedpan The various precipitating causes of heart failure were discussed Multiple pulmonary emboli were thought to be present—perhaps secondary to a right sided bacterial endocarditis Autopsy revealed CALCIFIC AORTIC MITRAL AND TRICUSPID STENOSIS organizing mural thrombi in the heart and emboli in the pulmonary and splenic arteries with multiple infarcts of lungs and spleen

X

(#601839 Admitted March 27 1952 Died March 28 1952)

(*Continued from page 586*)

DISCUSSION The patient had apparently been in relatively good health until nine weeks before death although it was stated that her color had been sallow for several years She developed malaise and gastrointestinal symptoms and later nose bleeds These symptoms with the finding of a blood nonprotein nitrogen of 214 mg % and phosphorus of 18 5 mg % make it altogether likely that this patient suffered from uremia and that this was responsible for the symptoms which developed nine weeks before death Furthermore since loss of blood was not a prominent manifestation the severe anemia was probably the result of the uremia The spectrum of findings indicates that the patient had chronic renal insufficiency She was probably given a sulfonamide a short while before admission but prior to the onset of her symptoms there was no history of any exposure to drugs or toxic substances of any sort In view of the very low level of serum calcium the possibility of hyperparathyroidism as a factor in the renal insufficiency seems unlikely

The major diagnostic problem in this case is the determination of the cause of the chronic renal insufficiency It is always important in cases of this type to be certain that there is no chronic low grade obstruction of the lower urinary tract Careful examination of the pelvic organs by the gynecological consultant disclosed no abnormalities One reason for paying particular attention to this possibility is the fact that she developed potassium intoxication Although

severe potassium retention may be seen during the terminal phase of oliguria in any type of renal disease we have been particularly impressed by its occurrence in patients with low grade obstruction of the lower urinary tract and therefore its presence always excites suspicion of this possibility However I think there is sufficient evidence to discard this possibility here The very low specific gravity of the urine leaves little doubt that the renal failure was due to disease of the kidneys

Did this patient have a diffuse or a circumscribed type of renal lesion and what is the significance of the fact that the blood pressure was not significantly elevated? It is true that she had symptoms suggesting uremia for only nine weeks before death but it was stated that her color had been sallow for several years In view of the severe anemia and the fact that no casts were seen and no albumin was present in the urine it would seem likely that this patient had a chronic renal disease of the circumscribed type In this category there are three important conditions to be considered (1) Arteriosclerosis of the renal vessels Although this may occur at an early age it would be unusual for it to affect the kidneys in such severe degree at the age of 45 This would seem a less likely diagnosis than the two remaining possibilities (2) Chronic contracted kidneys as a result of pyelonephritis This disease occurs in young adults who may not have evidence of chronic cystitis or of gross urinary tract obstruction The gradual reduction in the amount of relatively normal renal tissue sooner or later leads to restriction of kidney function Hypertension of a high degree appears in at least half of the cases but the pressure may remain normal The course may be practically symptomless or characterized by attacks of pyuria accompanied by lumbar pain with or without fever These patients rarely have edema unless cardiac failure appears It seems difficult in this case to distinguish between this diagnosis and the remaining one (3) Polycystic disease Patients with congenital polycystic disease of the kidneys usually die early in life but if they survive infancy they frequently enjoy good health until the age of 40 to 50 years In many of the cases one or another kidney can be palpated and the description here by one observer that several nodular masses could be felt and that there was dullness in the flanks certainly suggests this possibility Also not infrequently hemorrhages appear in the cysts and the patient may develop gross hematuria as was the case here On the other hand in most of the cases that I have seen at this stage of the illness some hypertension was present

I can see no reason to consider seriously the possibility of any of the types of diffuse renal disease associated with uremia and a normal blood pressure There was no evidence of bacterial endocarditis amyloid disease or myeloma kidney The latter diagnosis might be thought of because of the severe anemia Another possible explanation for the hematuria is that the patient developed a sulfonamide reaction with involvement of the kidney The two most likely possibilities are chronic pyelonephritis and congenital polycystic disease The course of the illness the findings and the age of the patient all favor the latter

As previously pointed out the final event which renders the small amount of remaining renal tissue functionless in a patient with polycystic kidneys is either infection or arteriolosclerosis with hypertension I would expect from the normal blood pressure and the *Aerobacter aerogenes* and white cells in the urine that infection was responsible in this case

Anatomical Diagnosis (Autopsy No 23576) Polycystic kidneys and liver Acute and chronic pyelonephritis Chronic cystitis Tubular degeneration adrenals History of uremia Diffuse wasserhelle cell change parathyroid Osteitis fibrosa Acute bronchitis Pulmonary edema Emphysema Hemorrhage epicardial fat Hemosiderin deposits spleen Epithelioid cell tubercles spleen Cystic disease breast Inspissated material pancreatic ducts with dilatation of pancreatic ducts and acini Hyperplasia femoral marrow Atrophy and melanosis of skin

In the liver there were several thin walled cysts beneath the capsule many of which were multilobular The kidneys were completely replaced by huge masses of cysts and showed the typical architecture of polycystic kidneys Almost no solid parenchyma could be identified on either side

Histologically the kidneys showed the typical appearance of polycystic disease in addition many of the cysts were filled with purulent exudate There was a well marked pyelitis That this infection was more than local is suggested by the presence of prominent tubular change in the adrenal cortex Mild osteitis fibrosa was present There was severe pulmonary edema

Summary This 45 year-old Polish woman who had had a sallow appearance for several years developed malaise and nausea and vomiting 9 weeks before death She was in severe uremia without hypertension or albuminuria but with marked pyuria gross hematuria and *A aerogenes* on urine culture One observer felt nodular masses throughout the abdomen The clinical picture was that of a circumscribed type of renal disease and a diagnosis of CONGENITAL POLYCYSTIC DISEASE OF THE KIDNEYS was made Although the kidneys were found to be almost replaced by huge masses of cysts there was a severe pyelitis and pyelonephritis which undoubtedly precipitated the terminal event

XI

(#125441 Admitted December 11 1951 Died January 15 1952)

(*Continued from page 589*)

DISCUSSION This patient was followed in this hospital for a period of almost 20 years He was very ill during the course of his final illness and a precise description of the pain could not be obtained As one reviews the over all course of his illness, certain facts of interest evolve for which we would like to find a satisfactory explanation When he was first seen in 1932 he had hypertension which persisted throughout the years In 1937 the urine was normal In July, 1949 he developed a left hemiplegia with hemihypesthesia and hemianopsia For several years he had complained of pains in his back which he stated were worse after this episode in 1949 On December 10 1951 he complained of severe pain in his hips legs back and right flank The urine contained red cells white cells casts and albumin Marked enlargement of the heart and numerous extra systoles were noted The following day the abdominal pain was less severe but he complained of a crushing precordial sensation which radiated down his left arm The blood pressure was 142/100 and on the following day it was 120/80 Five days later a questionable friction rub was heard over the precordium He had some fever but then improved The blood pressure remained around 150/95, and he was ready to go home on December 21 when he again had fever and developed signs suggesting consolidation at the right lung base At that time he was transferred to the Medical Service where he was found to be undernourished and grimaced with pain on any motion involving the left leg or lumbar spine He had a severe anemia The nonprotein nitrogen was normal and the phenolsulfonphthalein excretion was 80% in 2 hours Another finding of significance was the serum globulin of 6 8 gm % He continued to complain of pain The urine contained numerous white cells and from it *A aerogenes* was cultured He was started on a sulfonamide On December 31 it was noted that his nonprotein nitrogen was 60 mg % Following this his urinary output was reduced and there was a steady rise in the nonprotein nitrogen which reached over 200 mg % before his death During this time he developed an acidosis with phosphorus retention and at times a low serum sodium Of particular note in the x rays were the bones of the pelvis which showed some mottling

As one reviews these facts it would seem most difficult to put them all together under one diagnosis The long standing hypertension followed by the almost normal pressure during his final illness and the development of rapidly progressing uremia would seem difficult to explain on the same basis as the high serum globulin the anemia and the changes in the bones of the pelvis However numerous interesting possibilities arise

First let us consider the cause of the *high serum globulin* Acute and chronic infections of various sorts may be associated with a rise in the serum globulin level these include pneumonitis osteomyelitis pulmonary abscess syphilis lymphopathia venereum tuberculosis malaria and bacterial endocarditis Of this group it seems likely that we must set aside tuberculosis or bacterial endocarditis as possible diagnoses to be considered In the group of granulomatous diseases sarcoidosis and Schuller Christian disease must receive consideration since they may produce bone lesions as well as renal involvement Prominent for consideration in view of the bizarre character of the pain the anemia the renal failure and the high globulin is multiple myeloma It is also conceivable that with the high globulin and the bone lesions some neoplasm with metastases to bone might be present This might explain the anemia with young red cells in the peripheral blood

Now let us look further into the possible causes of the pain in the back abdomen and precordial area This pain may have been due to spinal involvement possibly as a result of tuberculosis tumor formation retroperitoneal sarcoma aneurysm—either saccular or dissecting periarteritis nodosa coronary occlusion with subsequent embolic phenomena bacterial endocarditis with embolic phenomena or thrombosis of the aorta Certain of these diseases might also result in a high serum globulin

Let us next take up the question of the vascular disease with severe hypertension In view of its long existence and the absence of any early evidence of renal disease the hypertension was probably vascular in origin possibly associated with renal arteriosclerosis Other possibilities which must be considered are glomerulonephritis pyelonephritis coarctation of the aorta increased intracranial pressure adrenal tumor Cushing s syndrome or obstruction of a renal vessel due to embolism It certainly seems unlikely that the pre-existing hypertension had anything to do directly with the hyperglobulinemia or the bone lesions

It may be important at least to review those situations in which

after 20 years of high blood pressure an individual s pressure may become essentially normal This happened in the present case before the uremia developed There is nothing to indicate that it was the result of loss of blood It might have been due to some vascular accident such as a coronary thrombosis or a dissecting aneurysm One must think also of chronic tuberculosis with involvement of the adrenals and the development of Addison s disease A remote possi bility is that there was a sudden shutting off of hormonal discharge from a pheochromocytoma

One of the most interesting features of this case was the rapid de velopment of the uremia He received no transfusions or any other substances which might have been expected to produce renal dam age with the possible exception of the sulfonamide There was no evidence put forward that he had developed acute urinary retention or sudden bilateral ureteral obstruction The rapid onset of such severe azotemia would hardly be on a prerenal basis although at times his serum sodium was low It would seem a reasonable possi bility that it resulted from some vascular difficulty It would seem unlikely, in view of the essentially normal renal function at the time of his admission that the entire renal disorder could be attributed to disease of the kidneys associated with sarcoidosis Schuller Christian disease or multiple myeloma Whatever might have been the precipitating cause of the uremia I would suspect that there was some underlying vascular disease of the kidneys

Having listed a wide variety of possibilities by exploring certain of the outstanding manifestations of this patient s final illness we must now narrow down these possibilities to those which seem the most likely I do not find it possible to explain on the same basis all of the cardiovascular manifestations the high serum globulin the ane mia the long standing pain and the bone lesions The last four of these might logically be attributed to multiple myeloma The long standing hypertension the peculiar type of abdominal pain ter minally the precordial pain the questionable friction rub the drop in blood pressure to normal levels during the final illness and the rapidly progressive uremia all point to an underlying vascular dis ease the course of which was altered by some complication during the later stages of life The pain apparently began in the abdominal area and only later was felt in the precordial region Serial electro cardiograms never showed evidence of myocardial infarction and although he had fever leukocytosis was not recorded It would there fore seem unlikely that this man had had a coronary occlusion If

he had one might be inclined to attribute the later renal complications to embolism Another possibility is that as a result of long standing aortic arteriosclerosis he had developed a thrombosis of the aorta which finally extended to reach the level of the renal vessels precipitating the terminal uremia This would make it difficult to explain the precordial pain except on the basis of coronary artery disease which I believe he must have had in view of his previous history of anginal pain and the very large size of his heart In view of the diastolic murmur during the terminal illness the fever the anemia and the terminal renal failure one would also have to consider seriously the diagnosis of bacterial endocarditis with renal emboli or nephritis A blood culture was sterile which weakens but does not rule out this possibility The previous record of very high blood pressure and the pain in the abdomen legs hips and precordial region suggest the possibility of dissecting aneurysm A dissecting aneurysm may at times extend very gradually and could account for pain over a period of several weeks The renal failure might have been due to the final extension of the aneurysm with dissection of both renal arteries Somewhat against this possibility is the fact that pulsations were felt in both femoral arteries There is no reason I think to suggest the possibility of periarteritis nodosa except for the widespread nature of the changes

To me the most probable diagnoses from the point of view of the cardiovascular system are arterio and arteriolosclerosis and arterial hypertension with the development of a dissecting aneurysm to account for the aortic diastolic murmur and final involvement of the renal vessels leading to uremia The bone lesions the high serum globulin and the anemia must be on some other basis The first possibility I would list would be multiple myeloma the second Schuller Christian disease and the third sarcoidosis

ANATOMICAL DIAGNOSIS (Autopsy No 23427) History of hyperglobulinemia Multiple myeloma Replacement of rib and vertebral marrow by plasma cells Obstruction of renal tubules by protein casts History of uremia Fibroadenomas of prostate History of perineal prostatectomy Thrombosis of periprostatic veins Embolus in pulmonary artery right lower lobe Lobular pneumonia Generalized arteriosclerosis Old hemorrhages of right cerebrum level of mid limb of internal capsule History of hypertension Hypertrophy and dilatation of left ventricle Chronic cystitis

The heart was enlarged due to hypertrophy of the left ventricle In the upper lobe of the left lung there were numerous pus filled bronchioles with patchy consolidation The right upper lobe showed a similar but more

extensive process In the lower lobe there was a coiled thrombus filling one of the branches of the pulmonary artery The kidneys were greatly enlarged The surfaces were smooth and pale On section the cortex was wide with indistinct outlines There were large fresh thrombi in the periprostatic veins The vertebral marrow was mottled and virtually replaced by yellowish white material The cancellous bone was soft and fragile One rib was virtually replaced with some yellowish material

This was a case of multiple myeloma with extreme involvement of all the marrow except that of the femur with almost complete replacement by plasma cells The bone was rarefied except for a few small areas where there seemed to be an abnormal deposition of calcium The kidney showed normal glomeruli but there were casts in many tubules and marked dilatation of tubules There was damage to the tubular epithelium about the numerous casts In places the epithelium was necrotic or completely lost

SUMMARY This 63 year old Negro man who had been known to have severe hypertension for 20 years and had a hemiparesis developed vague pains which became severe just before admission to the hospital At that time he had a peculiar febrile illness with chest and abdominal pain a fall in blood pressure and signs of pulmonary consolidation There were loss of weight anemia hyperglobulinemia and changes in the pelvic bones on x ray examination which coupled with the pains in the bones led to a diagnosis of myelomatosis To explain some of the cardiovascular manifestations and the sudden renal failure a diagnosis of dissecting aneurysm was also made At autopsy he had thrombi in the periprostatic veins and a pulmonary embolus and lobular pneumonia as well The basic disease was a PLASMA CELL MYELOMA There was generalized arteriosclerosis The cause of the sudden renal failure remains somewhat obscure unless it could be attributed to the changes in the tubules

LABORATORY VALUES OF CLINICAL IMPORTANCE (ADULT)

Blood—Chemical Constituents

(Values refer to ranges within which 90/ of normal persons are expected to fall)

Albumin serum $[(NH_4) SO_4]$	4 0–5 5 gm /100 ml
Amylase—reducing units	90–290 mg /100 ml
Bilirubin total serum	<0 8 mg /100 ml
Calcium serum	9–11 5 mg /100 ml 4 5–5 8 mEq /L
Carbon dioxide capacity (combining power) serum venous	49–67 vol / 22–30 mEq /L
Chlorides serum (as Cl)	348–384 mg /100 ml 98–108 mEq /L
Cholesterol	150–275 mg /100 ml
Creatine	1–2 mg /100 ml
Globulins serum $[(NH_4)_2SO_4]$	2 0–3 0 gm /100 ml
Hemoglobin males	14–18 gm /100 ml
females	12–16 gm /100 ml
Icteric index serum	4–7 units
Iodine protein bound serum	4–8 μ gm /100 ml
Nitrogen non protein serum	22–40 mg /100 ml
Phosphatase serum acid	<1 2 Bodansky units
alkaline	3–5 5 Bodansky units 5–12 King units
Phosphorus inorganic serum	3–4 5 mg /100 ml 1–1 3 mEq /L
Potassium serum	3 2–5 2 mEq /L
Proteins total serum	6–7 5 gm /100 ml
Sodium serum	132–148 mEq /L
Uric acid serum (Archibald)	2–6 mg /100 ml

Blood—Clinical Examinations

Cells	
Erythrocytes	4 2–5 5 million/cu mm
Leukocytes	5–10 thousand/cu mm
(differential count)	
Lymphocytes (1250–3500 per cu mm)	25–35%
Monocytes (200–1000 per cu mm)	4–10%
Neutrophils	
Juvenile (nonfilament) (150–1500 per cu mm)	3–15%
Segmented (2500–6500 per cu mm)	50–65%
Eosinophils (25–400 per cu mm)	0 5–4%
Basophils (0–200 per cu mm)	0–2%
Platelets	200–500 thousand/cu mm
Reticulocytes	0 5–2 0% red cells/cu mm
Clot retraction time •	1–3 hours
Coagulation time capillary blood	3–6 minutes
venous blood	5–20 minutes
Fragility of erythrocytes max resistance	0 32% NaCl
min resistance	0 42% NaCl
Hematocrit (volumes % of cells)	42–50
Hemoglobin males	14–18 gm /100 ml
females	12–16 gm /100 ml
Indexes of erythrocytes	
Mean Corpuscular Volume (cubic microns)	82–92
Mean Corpuscular Hemoglobin (micromicrograms)	28–32
Mean Corpuscular Hemoglobin Concentration (per cent)	32–36
Sedimentation rate (Wintrobe) males	0–9 mm in 1 hour
females	0–20 mm in 1 hour

Functional Tests

Bromsulfalein	No dye remaining in serum 45 min after injection of 5 mg per kg body weight
Cephalin flocculation	No precipitate
Concentration and dilution	Sp gr of urine after dry day 1 025 or more after water day 1 003 or less
Thymol turbidity test	4 units or less
Urea clearance	40 ml or more blood cleared per minute 75–125% of average normal

Urine

Urobilin	up to 1 20 dilution
Urobilinogen	<4 0 mg /24 hrs

Cerebrospinal Fluid

Cells	<5 per cu mm all lymphocytes
Chlorides as NaCl	120–130 mEq /L
Glucose	45–65 mg /100 ml
Protein	15–45 mg /100 ml
Pressure	100–200 mm water

Miscellaneous

	Average	Range
Circulation time (Decholin)	12 5 second	10–16 second

SPECIAL INDEX OF SYMPTOMS, SIGNS, AND LABORATORY FINDINGS

This index differs from the *General Index* in that it refers only to the case material It enables one to determine the frequency of certain clinical and laboratory findings and to review the variety of circumstances under which these are en ountered Only items which have seemed to have some pertinence have been included No attempt has been made to index detailed electrocardiographic or x ray findings The reference number indicates the first page of each case history in which the particular item is cited

GENERAL INDEX